# An investigation of the neuropsychological and neurobiological basis of conduct disorder problems in adolescence and the moderating effects of gender and callous-unemotional traits

Cattrell, Anna Louise

*Awarding institution:*
King's College London

# An Investigation of the Neuropsychological and Neurobiological Basis of Conduct Disorder Problems in Adolescence and the Moderating Effects of Gender and Callous-Unemotional Traits.

Anna Louise Cattrell

MRC Social, Genetic and Developmental Psychiatry Centre,

Institute of Psychiatry, King's College London

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## Abstract

This thesis aimed to identify the clinical, personality, neuropsychological and neurobiological characteristics associated with conduct disorder (CD) problems in a large cohort of community-recruited adolescents. Differences in these characteristics between males and females, and between those with high versus average 'callous-unemotional' (CU) traits, were examined.

The development of a proxy measure of CU is reported. This was used to explore whether high CU can be used to identify a sub-group of CD youths who differ from their peers in terms of clinical, personality and behavioural phenotypes in this community-recruited sample. Differences in emotional reactivity were investigated using an fMRI paradigm comparing neural responses to angry face stimuli. 'Cool' (cognitive) executive function was investigated using an fMRI task assessing motor response inhibition to a visually presented 'stop-signal' and a neuropsychological task assessing working memory. The third fMRI study explored 'hot' (motivation/affect) executive function using a paradigm investigating reward sensitivity to monetary values at different stages of reward processing (anticipation and outcome) and a neuropsychological task that investigated risk taking through a gambling paradigm. Between-group differences were investigated as a function of CD problems, gender and CU traits.

In terms of clinical measures males and females with CD were similar, although considering both CU and gender, in addition to CD, revealed differences in temperament. Emotional reactivity in the amygdala differed as a function of CD status in males, and CU traits differentiated a group of females who show heightened reactivity to negative stimuli. In terms of executive function there were differences as a function of CD and gender for both hot and cool executive function at the neurobiological and behavioural level. The findings are discussed in relation to current theories underlying the development of CD.

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## List of Acronyms

**AAL** Anatomical Automatic Labelling

**ACC** Anterior Cingulate Cortex

**ADHD** Attention Deficit Hyperactivity Disorder

**A-O** Adolescence-Onset Conduct Disorder

**AMYG** Amygdala

**APSD** Antisocial Process Screening Device

**ASPD** Antisocial Personality Disorder

**BA** Brodmann Area

**BAS** Behavioural Activation System

**BIS** Behavioural Inhibition System

**BOLD** Blood Oxygenation Level Dependent

**CANTAB** Cambridge Neuropsychological Test Automated Battery

**CD** Conduct Disorder

**CU** Callous Unemotional Traits

**DSLB** Digit Span Longest Backwards

**DSM-IV-TR** Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision

**EF** Executive Function

**E-O** CD Early-Onset Conduct Disorder

**EPI** Echo-Planar Imaging

**fMRI** Functional Magnetic Resonance Imaging

**FWE** Family Wise Error

**IFG** Inferior Frontal Gyrus

**INS** Insula

**IRI** Interpersonal Reactivity Index

**MarsBaR** MARSeille Boîte À Région d'Intérêt Toolbox for SPM

**MID** Monetary Incentive Delay

**MNI** Montreal Neurological Institute

**mOFC** Medial Orbitofrontal Cortex

**NAcc** Nucleus Accumbens

**NAS** Nonspecific Activation System

**NEO-PI-R** NEO Five Factor Personality Index Revised

**ODD** Oppositional Defiant Disorder

**OFC** Orbitofrontal Cortex

**PCL-YV** Psychopathy Checklist Youth-Version

**PFC** Prefrontal Cortex

**PIQ** Performance Intelligence Quotient

**ROI** Region of Interest

**RT** Reaction Time

**SD** Standard Deviation

**SDQ** Strengths and Difficulties Questionnaire

**SPM-8** Statistical Parametric Modelling, 8$^{th}$ Edition

**SPSS V.20** Statistical Product and Service Solutions Version 20

**SSRT** Stop Signal Reaction Time

**SST** Stop Signal Task

**SURPS** Substance Use Risk Profile Scale

**SWM** Spatial Working Memory

**U-O** Unspecified Onset Conduct Disorder

**VIQ** Verbal Intelligence Quotient

**vmPFC** Ventro-Medial Prefrontal Cortex

**VS** Ventral Striatum

**WCST** Wisconsen Card Sorting Task

**WISC-IV** Wechsler Intelligence Scale for Children, Fourth Edition

**3T** 3 Tesla

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## Declaration

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In the year before I began my PhD I worked full-time on the IMAGEN study at the Institute of Psychiatry. I was trained in all aspects of the IMAGEN Battery and completed the assessment of approximately 100 adolescents and their parents/guardians. I was responsible for the transfer of all London data to Neurospin. During my PhD I contributed to the visual quality control checks of the neuroimaging data. I also contributed to the development of the first follow up battery by performing language and comprehension checks on newly inserted measures. In the final stage of my PhD I took on managing the London site data collection for the second follow up assessment at age 18 and currently oversee the progress of all eight European assessment sites.

I performed all quality control examinations and all statistical analyses. This includes extracting region of interest data which were extracted by me on the basis of activation patterns from the data or by using the anatomical automated toolboxes available within the neuroimaging software package. All data collected for the IMAGEN project is available in a database to which collaborators have access. The work presented in this thesis is original and my own. Where information has been derived from other sources, I confirm it has been indicated in the thesis. This thesis has not been submitted for any other degree at another university.

# Chapter 1 Literature Review

## 1.1 Introduction to the Area

'Adolescence' refers to the period of time between child and adulthood, which is characterised by considerable physical, social and cognitive development. During adolescence there are marked increases in risk taking behaviour and poor decision making, that put the individual at heightened risk for developing maladaptive behaviours that may result in an increased risk for mortality (Abikoff & Klein, 1992). In addition, adolescence is regarded as a particularly delicate developmental period due to the extensive biological changes the brain goes through during this time (Giedd, 2004), which are critical for establishing normal adult brain function. There has been substantial research into adolescence and the extent to which behaviour during adolescence forms the basis for a physically and mentally healthy adult life. One of the risk factors for a suboptimal adulthood is externalising behaviour during adolescence such as conduct disorder problems, which are the subject of this thesis.

The present chapter first reviews research into the aetiology and outcomes associated with conduct disorder problems, and then addresses the extent to which the clinical profile and trajectory of conduct disorder problems manifests differently in males and females. This chapter then reviews current research into callous unemotional traits, which are characteristic of some individuals with conduct problems. Conduct disorder problems have been associated with difficulties in a number of domains such as emotional reactivity and executive function. This chapter reviews the evidence for these deficits addressing each domain in turn in terms of behavioural and functional magnetic resonance imaging data.

## 1.2 **Conduct Disorder**

Conduct Disorder (CD) is one of a constellation of disruptive behaviour disorders (also including Oppositional Defiant Disorder (ODD) and Attention Deficit Hyperactivity Disorder (ADHD)) that can give rise to significant antisocial behaviours. The Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision, DSM-IV-TR; American Psychiatric Association, 1994) defines Conduct Disorder as "a repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated". From a list of 15 symptoms at least three must be present during the previous year, and at least one present during the past month. Symptoms of CD fall into four categories; (i) Aggression to People or Animals (e.g., bullies, threatens or intimidates others, initiates physical fights, theft), (ii) Destruction of Property (e.g., deliberate destruction of others' property), (iii) Deceitfulness or Theft (e.g., lies to obtain goods or favours) and (iv) Serious Violations of Rules (e.g., truancy from school before 13 years old). The DSM-IV-TR makes a distinction between three types of CD; Early or Childhood-Onset (E-O), where at least one criterion characteristic of CD must be present prior to 10 years old, Adolescent-Onset (A-O); the absence of any criteria characteristic of conduct disorder before 10 years old, and Unspecified-Onset where the age of onset is unknown. The age of onset distinction for CD problems has been useful for researchers as a means to investigate the aetiology and developmental trajectory of CD. It has been shown that E-O CD is under strong genetic influence (Arseneault *et al.,*2003), and is associated with parent mental health problems and parent antisocial behaviour (McCabe, Hough, Wood, & Yeh, 2001). The A-O group is hypothesised to be more environmentally driven; so socialising as a teenager with a deviant peer group leads the adolescent into a similar pattern of rule-breaking antisocial behaviour characteristic of CD (McCabe *et al.,*2001). Irrespective of the age of onset, there are immediate costs of this disruptive disorder to the family and peer group and detrimental adult outcomes and potential societal costs if not successfully treated in youth.

***Mental Health Outcomes in Adulthood***

CD puts the individual at risk for the development of mental health problems such as substance use disorders by early adulthood (18 years old; Elkins, Mcgue & Iacono, 2007), and is associated with a greater risk for developing mood and disruptive disorders as an adult, compared with children who received no such diagnosis (Reef, van Meurs, Verhulst, & van der Ende, 2010). In addition, severe CD problems as a child have also been associated with relationship difficulties as an adult (Colman *et al.,*2009) including inter-partner conflict and dissatisfaction with the quality of the romantic relationship (Raudino, Woodward, Fergusson, & Horwood, 2012).

Using the age of onset classification for CD as described in the previous section, a seminal study by Moffitt and colleagues (2002) found that the two paths of antisocial behaviour (CD) were associated with different outcomes in adulthood. They found that Life-Course Persistent antisocial behaviour (E-O) was associated with elevated levels of psychopathic personality traits, violent and criminal behaviour, mental health problems and substance use in early adulthood (26 years old), while Adolescence-Limited (A-O) antisocial behaviour was associated with increased impulsive personality traits, mental health problems and substance use problems (Moffitt, Caspi, Harrington, & Milne, 2002). Both Life-Course Persistent and Adolescence-Limited antisocial behaviour were associated with criminal offending in adulthood, although the Life-Course Persistent group were more regular offenders and the crimes more severe. In particular Life-Course Persistent men were more violent than Adolescence-Limited men (Moffitt *et al.,*2002).

***Economic Outcomes in Adulthood***

A diagnosis of CD as a child/adolescent also has economic consequences for adulthood. Males with antisocial CD problems as a child (measured at 10 years old) were at greater risk for unemployment in adulthood (Knapp, King, Healey, & Thomass, 2011) and adolescents with CD have also been found to be more likely to leave school without qualifications, compared to their unaffected peers (Colman *et al.,*2009). In the same 2002 study (referred to previously) Moffitt and colleagues found that Life-Course Persistent men tended to be less educated, and achieved significantly lower status employment than Adolescence-Limited men. They also tended to receive more state benefits and had spent significantly more time unemployed than Adolescence-Limited men (Moffitt *et al.,*2002).

***Developmental Risk Factors for the Emergence of CD Problems***

A great many studies have explored the aetiology of conduct disorder problems reporting a number of risk factors for its development. A review of some of the larger longitudinal studies identified the following risk factors as some of the more consistent and pertinent for the development of CD; impulsivity, low IQ, childhood maltreatment, negative parenting practices (e.g. harsh discipline), parental relationship difficulties, parent antisocial behaviour and low socio-economic status (SES) (Murray & Farrington, 2010). A recent investigation by Oliver, Kretschmer & Maughan (2013) working with data from a large population based study, explored patterns of risk exposure and their relations to cognitive, emotional and behavioural outcomes in middle childhood. The authors identified four classes of risk; low risk, socio-demographic, family dysfunction and multiple risks. They found that children in the low risk group were significantly less likely to have clinical levels of CD problems compared to all other risk groups, and that the multiple risk group had the highest level of CD problems. The authors also found that the family dysfunction group had greater CD problems than the socio-demographic group.

Family level risk factors arising from characteristics of the parents, such as maternal psychopathology, may reflect the direct effect of the family environment on the behaviour. Barker *et al.,*(2012) investigated whether childhood exposure to risk factors associated with mental health problems increase the risk for childhood psychopathology beyond the effects of mothers being depressed. The authors found that children of depressed mothers were significantly more likely to be exposed to maternal-level risks such as early parenthood, low educational achievement, substance use and criminal behaviour, environmental risk factors such as low socioeconomic status, and family level risk factors such as low emotional and practical support networks, exposure to partner cruelty and being a single caregiver. Children of depressed mothers were at greater risk for the development of CD, ADHD and ODD and also anxiety and depression. The authors found that when they controlled for the cumulative effects of the risk factors, the direct effect of maternal depression on the development of CD, ADHD and ODD was reduced, but the exposure to maternal depression and cumulative risk factors remained significant predictors of externalising and internalising problems.

There is evidence to suggest that a history of CD problems in the mother puts them at risk for developing internalising symptoms such as depression during pregnancy, which were in turn a risk factor for their child becoming violent during adolescence (Hay, Pawlby, Waters, Perra, & Sharp, 2010). Further evidence for the intergenerational transmission of maltreatment and psychopathology have been presented by Plant and colleagues (2013) who found that in a sample of 125 families from a longitudinal community study, maternal childhood maltreatment (including physical, sexual and emotional abuse and neglect) was associated with exposure of their offspring to childhood maltreatment. Maternal childhood maltreatment was also significantly associated with maternal antenatal depression. The authors found that symptoms of disruptive behaviour disorders (CD, ODD, ADHD) in the offspring varied in

response to stress; children of mothers who experienced both maternal childhood maltreatment and antenatal depression showed significantly greater levels of childhood maltreatment compared to those who had not. The authors also reported that experiencing one of these risk factors independently, did not significantly increase the number of disruptive behaviour disorder symptoms. Childhood CD is also associated with parenting difficulties including the use of physical punishment, lower levels of parental warmth and inconsistent discipline (Colman *et al.,*2009), which are risk factors themselves for the development of CD in childhood.

The association between family level risk factors and the development of CD problems might be a consequence of both the parents' genes and the environment; representing a passive gene-environmental correlation. Bornovalova and colleagues (2013) presented research supporting both hypotheses; they found that both maternal and paternal parenting and marital problems had a direct environmental effect on the development of disruptive behaviour disorders such as CD. They also found that maternal and paternal antisocial behaviour was more strongly associated with disruptive behaviour disorders in biological families, rather than adoptive families which tend to not contain the same risk factors, indicating a passive gene-environmental route to conduct problems (Bornovalova *et al.,*2013).

A diagnosis of CD as a child or adolescent also has consequences for the next generation. The home environment appears to be particularly negatively affected; both Life-Course Persistent (E-O) and Adolescence-Limited (A-O) antisocial behaviour were associated with relationship dissatisfaction; Life-Course Persistent men used more controlling abuse against their partners compared to Adolescence-Limited men and were also more likely to use violence against their child when angry (Moffitt *et al.,*2002).

There is also some evidence to suggest that risk factors for the development of CD may act in a sex-specific way. Barker and colleagues (2011) found that prenatal risk factors such as low socioeconomic status, no partner, teen pregnancy, criminal behaviour, substance use, regular smoking, depression and anxiety significantly increased the risk of males developing externalising (CD, ODD, ADHD) and internalising (anxiety, depression) problems, and a decrease in verbal IQ ability in both males and females. Further evidence for sex differences in the development of CD comes from a large community sample of twins. Meier and colleagues (2011) used retrospective reports of conduct disorder symptoms and found results indicating that there were qualitative sex differences (either in genetic or shared environmental influences) in childhood conduct disorder; however the authors were unable to resolve whether these influences were sex-specific genetic influences or sex-specific shared environmental influences. Sex differences in CD problems are discussed in more detail in the next section.

***Sex Differences in Conduct Disorder***

A large body of the literature available on CD thus far has been concerned with CD problems in males; indeed males outnumber females in prevalence. In a population of 10,000 British children approximately 2.1 % of males and 0.8% of females were afflicted by CD according to DSM-IV criteria (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). Additionally the researchers found the risk for developing CD increased with age in males and females, although in females this rate was low until their teenage years.

Silverthorn and Frick (1999) proposed that conduct disorder problems in females tended to manifest during adolescence rather than in childhood, making the E-O/A-O distinction of the DSM-IV sub-optimal . They suggested that antisocial behaviours characteristic of CD problems

in females do not emerge until adolescence due to factors such as gender-stereotyping (females are expected to behave in a gender appropriate manner, therefore not aggressively or antisocially), and protective influences such as being seen as more socially and academically competent than males. As such they proposed that a female-specific trajectory should be incorporated into the classification system describing this 'delayed-onset'. However, since this initial proposition, the notion of a 'delayed-onset' route to conduct problems in females has been challenged by longitudinal research that was not available at the time of Silverthorn and Frick's proposal.

The Pittsburgh Girls Study is a longitudinal community recruited cohort of over two thousand females recruited in early childhood (between 5-8 years old) and followed up yearly until late adolescence or early adulthood (ages 17-20 years old). The specific aims of the study are to describe the conduct disorder phenotype in females and track its developmental course, identifying risk and protective factors associated with CD in females. Keenan and colleagues found that overall CD prevalence was between 5-9% at ages 7-14 years, and more than half of those who met the criteria for CD had shown at least three symptoms within a 12 month period before they were 10 years old, contradicting the delayed onset proposition. Keenan and colleagues proposed that one possible route to CD problems in females is due to an "exacerbation or intensification of symptoms from childhood to adolescence, rather than initiation or acute onset of CD during adolescence" (Keenan *et al.,*2010). The authors also reported that consistent with previous reports, CD problems were associated with harsh punishment and low parental warmth.

There is some evidence to suggest that childhood temperamental and behavioural profiles might act in a sex-specific way as risk factors for the development of CD problems in adolescence. Côté *et al.,*(2002) performed a longitudinal assessment of children from age 6

and found that boys were at significant risk for CD if they were hyperactive, hyperactive and unhelpful or hyperactive, fearless and unhelpful, while girls were at risk if they were both hyperactive and unhelpful (Cote, Tremblay, Nagin, Zoccolillo, & Vitaro, 2002). There is also some evidence suggesting that substance use associated with CD problems may also be determined in a sex-specific manner. A prospective longitudinal study by Pedersen and colleagues found serious conduct disorder problems had a moderate effect on cannabis initiation in boys, while aggressive and covert conduct problems had an effect on cannabis initiation in girls (Pedersen, Mastekaasa, & Wichstrom, 2001).

There is evidence to suggest that males and females are in fact at equal risk for developing negative adult outcomes. An influential study by Odgers and colleagues (2008) investigated the childhood origins and adult outcomes of antisocial behaviour and identified four trajectory groups; Low Antisocial Behaviour, Childhood-Limited, A-O and Life-Course Persistent. The authors demonstrated that although the number of males and females differed (n526 males compared to n494 females) the trajectory and outcomes associated with antisocial behaviour problems were very similar; in the Life-Course Persistent Group, males and females equally engaged in violent behaviour and reported significant mental and physical health problems and economic difficulties (Odgers *et al.,*2008). This finding was also supported by Bor and colleagues (2010) in their longitudinal community-based investigation of A-O and Life-Course Persistent males and females with antisocial behaviour (Bor, McGee, Hayatbakhsh, Dean, & Najman, 2010).

## 1.3 **Callous Unemotional Traits and Conduct Disorder**

***What are callous unemotional traits?***

Psychopathy is a personality trait and describes characteristics such as a lack of empathy and guilt, and shallow fast changing emotions, and was initially described by Hare (1970) and Cleckley (1976) in their observations of hospital inpatients. In 1994 the first piece of published research emerged that attempted to assess the construct of Psychopathy in children aged 6-13 years old in a developmentally appropriate way (Frick, Obrien, Wootton, & Mcburnett, 1994) . The work by Frick and colleagues identified two dimensions of behaviour in clinic-referred children and adolescents. The first identified a group that showed impulsive conduct problems and the second showed an interpersonal style associated with psychopathy; a 'callous-unemotional' group. The traits initially identified by Frick and colleagues included a lack of concern about schoolwork, a lack of guilt or remorse, shallow emotions, not showing emotions, superficial charm and lack of concern about the feelings of others (empathy).

Since this time callous unemotional (CU) traits have been used by researchers to identify a sub-group of individuals for whom antisocial behaviours, such as conduct disorder problems, are more pervasive and persistent and who show a different neurocognitive profile to those individuals with antisocial behaviour problems without CU traits. One of the first studies to investigate CU traits and antisocial behaviour was conducted by Christian and colleagues (1997). The authors identified four groups of children; (1) children with conduct problems and high CU traits, (2) children with high CU traits, (3) children with impulsive conduct problems and (4) controls. They found that the children with conduct problems who also had high CU traits showed greater numbers of aggressive symptoms compared to the conduct problems only group (Christian, Frick, Hill, Tyler, & Frazer, 1997).

A number of scales have been developed to measure CU traits, two of the most commonly used are the Antisocial Process Screening Device (APSD; Frick & Hare, 2001) and Psychopathy Checklist Youth-Version (PCL-YV; Forth, Kosson & Hare, 2003). The APSD is a 20-item behaviour rating scale that can be completed by parents, teachers or the youth and is commonly used in community samples. Items pertaining to CU in the APSD include 'unconcerned about schoolwork', 'does not feel bad or guilty', 'emotions seem shallow', 'does not show emotions', 'acts charming in a way that seems insincere' and 'is unconcerned about the feelings of others'. The PCL-YV is a clinician administered interview and is used primarily with clinical groups. Items referring to CU in this scale are very similar to the APSD and include a lack of remorse, shallow affect, a callous lack of empathy and failure to accept responsibility.

***Developmental Risk Factors for the Emergence of CU Traits***

There is evidence to suggest that CU traits might be genetically determined, with compelling evidence originating from two sets of analyses on a large sample of twin pairs. The first investigation found that CU traits are under strong genetic influence, and when present in children who also had antisocial behaviour was highly heritable (Viding, Blair, Moffitt, & Plomin, 2005). The second showed that there was substantial genetic overlap between both CU and CD problems in males and females, and the authors suggest that there may be genes common to both conditions driving this effect (Viding, Frick & Plomin, 2007). Other researchers have explored family-level risk factors for the development of CU traits. Barker and colleagues (2011) investigated the role of prenatal maternal risk, temperament and parenting on the development of CU traits in a longitudinal population-based study. The authors found that children with both conduct disorder problems and high CU were from lower socioeconomic environments, experienced greater levels of maternal psychopathology, partner cruelty toward the mother, harsh parenting and the mother reporting they did not enjoy their child.

Fontaine and colleagues (2010) investigated the etiology of developmental trajectories for CU traits using a longitudinal study of twin pairs. The authors identified four trajectory groups; Stable High, Increasing, Decreasing and Stable Low. They found that children in the stable high group showed the most difficult child behaviour and family background. Children in the increasing and decreasing trajectory groups showed more negative child behaviour, family problems and had more negative outcomes compared to the children in the stable low group, and those children in the increasing trajectory group showed greater conduct and hyperactivity problems compared to children in the stable low group.

Cornell and Frick (2007) investigated the interaction between parenting style and child temperament in young children aged between 3-5 years old. They found that behaviourally inhibited children scored higher on a parent-rated index of moral conscience (guilt) and that this effect was also moderated by parenting variables. In behaviourally uninhibited children greater levels of inconsistent discipline led to lower parent ratings of guilt, and greater authoritarian parenting led to higher parent ratings of guilt. The authors also found that in behaviourally uninhibited children greater inconsistency in parent discipline was negatively related to empathy. This study suggests that inconsistent parenting characteristics may be associated with aberrant moral and conscience development which may contribute in itself to the development of CU traits.

Dadds *et al.,*(2012) investigated the developmental origins of callous-unemotional traits in a sample of young children (age 4-8 years) and found that children with conduct disorder problems and high CU traits showed significantly lower levels of reciprocal verbal and physical affection compared to children with conduct disorder problems and low CU traits and control children. The authors also found that children with high CU traits showed less eye contact with their primary attachment figure. The authors suggested that rearing a child who is rarely

affectionate may discourage parents from affectionate behaviour and that impaired eye contact behaviour may represent the absence of a basic factor underlying social and moral development. Taken together these studies suggest that there may be multiple pathways for the development of CU traits; a genetic predisposition, perhaps coupled with increased family level risk factors and parenting styles. The trend for assessing these traits has increased only recently, and the next section further discusses the clinical utility of knowing about CU traits.

***What is the clinical and/or predictive utility of knowing about callous unemotional traits?***

Callous Unemotional (CU) traits appear to not only delineate a group of individuals for whom antisocial behaviour problems are worse, but may also be used to predict outcome. This suggests that knowing about CU trait levels, particularly high levels, might have clinical utility when treating patients with CD. CU traits are now considered so important that they have been included as a specifier under the Conduct Disorder section of the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The specifier was designed to apply to those persons who have a relatively more severe form of the disorder who require different treatment interventions, and reflects the individual's limited prosociality such as empathy and guilt (see www.DSM5.org for further information).

A population-based investigation of children and adolescents suggested that CU traits were associated with the level of Conduct, Hyperactivity and Emotional problems and also the negative impact those problems had on the family (Moran, Ford, Butler, & Goodman, 2008). A longitudinal investigation by Pardini and colleagues (2012) found that females with both CD and CU showed more externalising symptoms, bullying and relational aggression compared to females with CD only, and found that across a six year period the females with CD and CU traits showed more problematic clinical symptoms and behavioural problems (Pardini, Frick, &

Moffitt, 2010). Wymbs and colleagues (2012) showed that males with both CD and CU problems showed significantly more negative outcomes (problematic substance use) by early adolescence (Wymbs *et al.,*2012), and CU traits at age 13 were associated with increased juvenile and adult arrests and early adulthood antisocial personality disorder problems (McMahon, Witkiewitz, Kotler, & Gr, 2010). There is also evidence that incarcerated offenders with high CU traits had a greater number of sexual offense victims and used more violence against their victims than offenders low on CU traits (Lawing, Frick, & Cruise, 2010). The study previously mentioned by Christian and colleagues (1997) found that CU traits in their group of children without co-occurring antisocial behaviour was associated with significantly greater risk of school suspensions compared to controls. Taken together these findings suggest that not only does CU exacerbate antisocial behaviour problems, but also suggests that CU, independent of antisocial behaviour problems, is a risk factor for negative outcomes.

***Are there gender-specific differences in the prevalence and trajectory of callous unemotional traits?***

As the momentum surrounding the practical and clinical utility of assessing CU traits continues to grow, so has work investigating whether there are differences in the prevalence and trajectory of the CU trait as a function of gender. Research has identified that males are more affected than females by CU traits, a finding that is consistent over a number of years across both community and clinical samples, see Table 1. Males consistently rate themselves, and are rated by others, as showing higher levels of CU traits compared to females.

Table 1 Sex Differences in CU Traits

| Authors | Measure | Age | Sample | Gender Differences |
|---|---|---|---|---|
| Marsee, Silverthorn, and Frick (2005) | APSD | 10-17 years | Community N=200 (M86 F114) | Males > Females [teacher and self-rated] |
| Krischer and Sevecke (2008) | PCL-YV | 14-19 years | Incarcerated Juvenile N=185 (M96 F89) | Males > Females [researcher rated] |
| Moran, Ford, Butler & Goodman (2008) | 7 items similar to APSD | 5-16 years | Community N=5770 | CU significantly associated with being Male [Teacher rated] |
| Frick, Cornell, Bodin, Dane, Barry & Loney (2003) | APSD | Average age 12.36 (SD 1.73) | Community N=100 (M53 F47) | Males > Females [Parent & Teacher rated] |
| Frick, Bodin & Barry (2000) | APSD | Average age 10.65 (SD 1.6) | Community N=1136 (M534 F602) | Males > Females [Parent & Teacher] |
| Pechorro, Viera, Poiares, Viera, Maraco, Neves & Nunes (2013) | APSD | 13-20 years | Incarcerated Juvenile N=261 (M217 F44) | Males > Females [Self-rated] |
| Wymbs, McCarty, King, McCauley, Vander Stoep, Baer & Wasbusch (2012) | APSD | 11-15 years | Community N=516 (M266 F 250) | Males > Females [Self and Parent rated] |

APSD Antisocial Process Screening Device, (Frick & Hare, 2001) 20-item measure of antisocial behaviour in children, suitable for use with community samples

PCL-YV Psychopathy Checklist Youth Version (Forth, Kosson & Hare, 2003) typically used with clinical/incarcerated population

Fontaine and colleagues found no gender-specific effects in the trajectory for conduct problems and CU traits (Fontaine, McCrory, Boivin, Moffitt, & Viding, 2011), however there is evidence to suggest that while developmental trajectory might not differ as a function of gender, the temperamental, behavioural and clinical profiles might be different for males and females. Fearless temperament is a tendency toward behavioural disinhibition that has been previously linked to externalising symptoms (Colder, Mott, & Berman, 2002) and a reduced capacity to feel guilt; if you are not afraid of the consequences of your actions you are less likely to feel guilty about your bad behaviour. Barker and colleagues (2011) found that fearless temperament was associated with higher conduct problems and CU traits in both males and females, but the manifestation of this trait was different for males and females; males showed reduced sensitivity to punishment while females behaved boldly in novel situations and toward strangers (Barker, Oliver, Viding, Salekin, & Maughan, 2011). Conduct disorder problems with and without CU traits have been related to disruption in a variety of domains such as emotional processing and executive function ability. These difficulties are discussed in more detail in the following sections.

## 1.4 **Emotional Reactivity**

This section reviews some of the research studies that have suggested children and adolescents with conduct disorder problems with and without callous unemotional traits have difficulty processing their own, and other people's emotions. Evidence is reviewed from behavioural and functional magnetic resonance imaging (fMRI) emotion recognition paradigms.

***Why does it matter if people perceive emotions differently?***

Facial expressions are one of the most salient social cues and humans pay more attention to emotional rather than neutral expressions (Vuilleumier, 2005). Facial expressions of emotion can convey intent, the thoughts of another person, and give the 'reader' an insight into the state of mind of another individual. As such, humans base their actions largely on the interpretation of facial expressions of emotion. A welcoming smile signals it is safe to approach someone, while a fearful or angry expression might indicate it is time to flee. Emotional reactivity refers to a 'constellation of processes that serve to either amplify, attenuate, or maintain the strength of emotional reactions' (Davidson, 1998) and may be used as a pertinent marker to investigate aberrant behaviour associated with psychopathology. Behavioural difficulties associated with psychopathology in terms of emotion dysregulation may be a consequence of a person's inability to accurately express or control their reactions to the presentation of emotion (e.g. reading the face of another person in a social situation), or a failure to manage or monitor their own vicarious experience of emotion.

***Behavioural Evidence for Emotional Dysregulation in Conduct Disorder***

A considerable body of work has emerged documenting differences in emotional reactivity in individuals with CD problems, although the findings are mixed. There is evidence to suggest that there are physiological differences between CD people and unaffected controls. Males with CD with and without co-morbid Attention Deficit Hyperactivity Disorder (ADHD) reported lower levels of emotional response to unpleasant images and reduced autonomic responses (skin conductance and heart rate) across positive and negative emotional stimulus categories (Herpertz *et al.,*2005). Males with E-O and A-O CD showed a reduced capacity to acquire typical responses to a fear conditioned response, and showed reduced startle amplitudes across all emotional stimuli categories (Fairchild, Van Goozen, Stollery, & Goodyer, 2008). Males with E-O CD performed worse in an emotion recognition task for expressions of anger,

disgust and happiness, while A-O CD males performed worse for fear recognition compared to controls (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009). Fairchild and colleagues also found that compared with control subjects, females with CD were impaired for the recognition of anger and disgust, and showed reduced autonomic response (skin conductance response) to aversive unconditioned stimuli (Fairchild, Stobbe, van Goozen, Calder, & Goodyer, 2010) However a study published in the same year found no evidence for such a disadvantage in emotion recognition in females with CD (Pajer, Leininger, & Gardner, 2010).

***fMRI Evidence for Emotional Dysregulation in Conduct Disorder***

There is also an emerging body of evidence suggesting that the aberrant emotional responses observed in the behavioural studies have an extensive neural basis, although again the findings are mixed. Male adolescents with E-O/A-O CD showed reduced brain responses in regions critical for socio-emotional processing including the amygdala, ventro-medial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC) and insula when viewing angry vs. neutral faces, and the E-O group showed further reductions in activation in the bilateral amygdala when viewing sad vs. neutral faces. Unusually the authors found increased amygdala responses to neutral but not angry faces in both E-O and A-O adolescents compared to controls. The authors attributed this finding to increased vigilance in response to ambiguous stimuli (Passamonti *et al.,*2010). Conversely E-O CD males showed increased left amygdala activation in response to negative compared to neutrally valenced pictures leading the authors to suggest that this group might in fact be more sensitive to environmental cues than controls (Herpertz *et al.,*2008).

***Behavioural Evidence for Emotional Dysregulation in Conduct Disorder with Callous Unemotional traits***

In addition to evidence documenting aberrant emotional reactivity in CD, a considerable body of work has found individuals with psychopathy/CU traits also show deficits in processing emotional stimuli. Early work by Blair and colleagues found a reduction in a physiological measure (electrodermal skin response) in response to distressing emotional cues (images of crying children and adults) in psychopathic compared to control adult male inmates (R. J. Blair, Jones, Clark, & Smith, 1997). One of the most consistent findings across study populations has been that individuals who score high for psychopathic/CU traits are impaired at recognising emotional expressions of fear, compared to individuals without high psychopathic/CU traits (Blair, Colledge, Murray, & Mitchell, 2001; Fairchild, Van Goozen, Calder *et al.,*2009; Fairchild *et al.,*2010). This recognition deficit also extends to auditory processing; both male children and adults with high trait psychopathy/CU scores were impaired at attributing fear during emotional prosody recognition tasks, compared to participants without high trait psychopathy/CU (Stevens, Charman, & Blair, 2001; Blair *et al.,*2002). It is not only the recognition of fear that is impaired in children and adolescents with psychopathic traits but also the subjective experience of fear. Children and adolescents with psychopathic traits (males and females) reported fewer symptoms of sympathetic arousal (e.g. breathing changes, accelerated heartbeat, shaking, sweating or feeling tense) during emotionally evocative situations experienced by the participant that would normally evoke a fearful response (Marsh *et al.,*2011).

***fMRI Evidence for Emotional Dysregulation in Conduct Disorder with Callous Unemotional traits***

Evidence from fMRI investigations have shown that individuals with psychopathic/CU traits also demonstrate aberrant neural responses in regions crucial for socio-emotional processing

of emotional stimuli. Research has consistently found that adolescents with CD/ODD plus high CU traits exhibit reduced amygdala reactivity in response to the presentation of fearful faces (Jones, Laurens, Herba, Barker, & Viding, 2009; Marsh *et al.,*2008). Adolescent males and females with CD/ODD and high psychopathic traits showed reduced activity in areas involved in empathy processing (anterior cingulate cortex, amygdala and ventral striatum) during a pain perception task where the adolescents imagined the pain depicted had happened to themselves or someone else. Reductions in amygdala response were particularly associated with pain perceived to be happening to another person (Marsh *et al.,*2013).

***Structural differences associated with Conduct Disorder and Callous Unemotional traits***

In addition to functional differences in brain reactivity in response to emotional stimuli, there is also evidence for structural differences in the brain anatomy of CD youths, compared to unaffected control participants. Reductions in gray matter volume have been found in the temporal lobe in youths with E-O CD (Kruesi, Casanova, Mannheim, & Johnson-Bilder, 2004), sub-cortical temporal regions (amygdala) in E-O and A-O CD males compared to controls (Fairchild *et al.,*2011) and E-O CD males showed reduced gray matter volumes in the left orbitofrontal region, and bilaterally in the temporal lobes, including the left amygdala and hippocampus (Huebner *et al.,*2008). A recent study by Fairchild and colleagues (2012) has shown female adolescents with CD also show reductions in gray matter volume in the bilateral insula and right ventral striatum compared to controls. These differences are also different to those observed by the same research group in a comparison group of CD males. The authors found a sex-by-diagnosis interaction in the bilateral anterior insula; CD females had reduced volume compared to control females, while CD males had increased insula volume compared to control males (Fairchild *et al.,*2012).

Volumetric differences in brain structure have also been identified in clinical groups with psychopathy. Male offenders with antisocial personality disorder (ASPD) with psychopathy showed reduced gray matter volumes in the prefrontal cortex and temporal poles compared to ASPD patients without psychopathy and controls (Gregory *et al.,*2012). Anatomical brain structure matters greatly; reduced volumes in gray matter might contribute to the aberrant emotion processing observed in this group compared to controls. If there are reductions in areas known to be involved in socio-emotional learning this could compromise the ability of the individual to learn and practise socially acceptable norms in terms of emotion recognition and responses to those emotions. These volumetric differences may not only contribute to aberrant emotion processing, but also other domains including executive function. Evidence supporting this notion is supported in the next section.

## 1.5 **Executive Function**

This section will review research studies that have suggested children and adolescents with conduct disorder problems with and without callous unemotional traits show deficits across executive function abilities such as decision making and risk taking, reward and punishment sensitivity, working memory and inhibitory control. Evidence is reviewed from behavioural and functional magnetic resonance imaging (fMRI) emotion recognition paradigms.

### ***What is Executive Function?***

Executive function is a multifaceted construct that covers many abilities such as self-control and self-monitoring, planning, selective attention, working memory, task switching, decision making and inhibition, see Jurado and Rosselli (2007) for a review. Difficulties in any one of these higher-order domains can mean an individual is at risk for engaging in undesirable behaviour, putting themselves, and sometimes others at risk. For instance, individuals who

have difficulty with action control can have difficulty stopping a behaviour once they are engaged in it (response perseveration) which is possibly a consequence of an inability to switch between specified response contingencies. Other individuals find it difficult to inhibit a response when cued to do so (inhibitory control). Executive function abilities do not operate in isolation and can contribute to deficits in adaptive behaviour, communication and socialisation (Clark, Prior, & Kinsella, 2002), making them a pertinent marker to investigate in CD.

### *Hot and Cool Executive Function*

Two aspects of executive function (EF) have been identified by researchers; 'hot' and 'cool', see Rubia (2011). 'Hot' EF is primarily concerned with affect and motivation, while 'cool' EF is more cognitive. At the neural level, 'hot' EF is associated with ventral and medial regions of the prefrontal cortex and sub-cortical basal ganglia regions (e.g. caudate, putamen, pallidum and nucleus accumbens) (Liu, Hairston, Schrier, & Fan, 2011). 'Cool' EF is more associated with dorsolateral regions of the prefrontal cortex including the middle frontal gyrus, inferior frontal gyrus and superior frontal gyrus (Swick, Ashley, & Turken, 2011).

### *Behavioural Evidence for Hot Executive Dysfunction in Conduct Disorder (and psychopathy/callous unemotional traits)*

An increasing body of evidence has documented aspects of 'hot' EF that are disrupted in CD. One of the most consistent findings is that youths with CD tend to make more risky decisions and appear to be reward 'biased' at the same time as being punishment 'insensitive'. Research has shown that male offenders tended to gamble more than control participants, choosing the more risky option, and did so even after a small win; whereas controls gambled least after receiving a small win (Syngelaki, Moore, Savage, Fairchild, & Van Goozen, 2009). A similar effect was also found in a group of male and female Oppositional Defiant Disorder (ODD)

children (age 7-12 years old). The authors found that the ODD children preferentially chose the condition that carried frequent large rewards, despite the fact that this condition also contained increasing penalties (Luman, Sergeant, Knol, & Oosterlaan, 2010). Studies have also shown that CD/ODD is associated with punishment insensitivity. Matthys and colleagues found that males with CD/ODD continued to make the same decision despite the reward contingency having changed to punishment (Matthys, van Goozen, Snoek, & van Engeland, 2004), a finding that is also common to individuals with psychopathic traits. Newman and Kosson (1986) found that incarcerated males with psychopathic traits made significantly more errors than control participants in a passive-avoidance task, specifically during the condition where a previously rewarded stimulus became punished(Newman & Kosson, 1986). This evidence suggests that both CD problems and high CU/trait psychopathy may confer a liability for disrupted 'hot' EF in terms of decision making, and also appear to show aberrant reinforcement signalling; both groups appear to show a preference for reward and insensitivity to punishing stimuli.

***fMRI Evidence for Hot Executive Dysfunction in Conduct Disorder (and psychopathy/callous unemotional traits)***

The behavioural evidence presented in the previous section is supplemented by additional work that has examined the neural basis for these dysfunctions, although the findings are quite mixed. A study by Bjork and colleagues (2010) suggested that ODD/CD adolescents were especially sensitive to rewarding trial outcomes, supporting the notion that this group are 'reward-oriented'. The authors found that ODD/ODD+CD adolescents (male and female) showed no significant between-group differences in activation of reward related regions (nucleus accumbens) compared to controls during reward anticipation. However, during the notification of a rewarded trial the ODD/ODD+ADHD group showed greater ventral striatal (including nucleus accumbens) activation, and during the notification of no reward showed greater deactivation of the ventral striatum compared to controls (Bjork, Chen, Smith, &

Hommer, 2010). A study by Gatzke-Kopp and colleagues(2009) has suggested that this finding might not always be consistent; the authors found no differences in striatal response during the receipt of reward in CD/CD+ADHD males compared to controls (Gatzke-Kopp *et al.,*2009). However, during a reward omission phase while control participants' activity was transferred to the anterior cingulate cortex (ACC; a region implicated for the processing of punishment) the CD/CD+ADHD participants failed to recruit the ACC and continued to show activation of the striatum. The authors suggest this could be evidence to explain why this group continue to respond to stimuli even when rewards are withdrawn.

Evidence also exists suggesting that individuals with psychopathic personality traits also show disrupted reinforcement signalling at the neural level. Bjork and colleagues (2012) found that in control cases without clinical psychopathy or antisocial behavioural disorder, psychopathic personality traits were associated with heightened neural sensitivity to rewarding stimuli (Bjork, Chen, & Hommer, 2012). Further evidence was presented by Finger and colleagues (2011). The authors found that youths with CD/ODD and high psychopathic traits showed disruption (less reactivity compared to controls) in areas important for value representation and reward processing; orbitofrontal cortex and caudate (Finger *et al.,*2011). Taken together with the behavioural work, 'hot' executive dysfunction in decision making and reward sensitivity appears to be characteristic of individuals with CD, both with and without CU traits.

***Behavioural Evidence for Cool Executive Dysfunction in Conduct Disorder (and psychopathy/callous unemotional traits)***

There is evidence to suggest that 'cool' executive functions are also disrupted in CD and the associated Disrupted Behaviour Disorders (Attention-Deficit/Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD)). Pajer and colleagues (2008) showed that overall

neuropsychological function (indexed by full IQ score) was impaired in girls with CD compared to controls (Pajer *et al.,*2008). Evidence for impaired set-shifting ability, how well a person can adapt their behaviour to changing levels of reinforcement, has also been shown to be impaired in CD with most evidence coming from the Wisconsen Card Sorting Task (WCST). Controls consistently make fewer perseverative errors than male offenders (aged 12-18 years old) (Syngelaki *et al.,*2009), male CD adolescents (Lueger & Gill, 1990) or CD children (aged 7-12 years old), even when the authors controlled for the effects of ADHD symptoms and socio-economic status (Toupin, Dery, Pauze, Mercier, & Fortin, 2000). Spatial working memory (SWM) deficits have also been observed in CD participants; specifically this group make more between-search errors (searching for a target stimulus in an area where a target has previously already been found). This effect has been shown in male offenders (Syngelaki *et al.,*2009); (Cauffman, Steinberg, & Piquero, 2005), and in an ADHD+CD/ODD group of children (Barnett, Maruff, & Vance, 2009). Finally, there is evidence that CD is associated with deficits in inhibitory control, although the findings are mixed. Schoemaker *et al.,* (2012) found that ODD/CD children (aged 3.5-5.5 years old) were worse at inhibiting their responses during a Go/No-Go Task compared to controls, although when ADHD symptoms were additionally controlled for the effect was no longer significant (Schoemaker *et al.,*2012). Adolescent data are less clear; Dougherty *et al.,*(2003) found adolescent inpatients with Disruptive Behaviour Disorders were less able to inhibit their response to a stop signal than controls (Dougherty *et al.,*2003), however evidence presented by Dolan and Lennox (2013) found no evidence for such a disadvantage in their adolescent CD/CD+ADHD group.

***fMRI Evidence for Cool Executive Dysfunction in Conduct Disorder (and psychopathy/callous unemotional traits)***

Relatively few studies have been conducted exclusively examining the neurobiological basis of 'cool' EF in CD; the majority of studies have focused on 'hot' EF. One of the few studies that

did, examined interference inhibition and selective attention using a task measuring the 'Simon Effect' (the tendency to react faster and more accurately to a target stimulus presented in the same relative location as an initial cued stimulus). The authors found that CD and ADHD adolescent males showed significantly less reactivity in the right superior and middle temporal lobe and right precuneus during interference inhibition in incongruent trials, and less reactivity during congruent oddball trials in the right dorsomedial prefrontal cortex (Rubia *et al.,*2009). This was one of the first studies to identify aberrant patterns in neural reactivity in response to a 'cool' cognitive task in adolescents with CD that had previously only been shown to be impaired in adolescents with ADHD. This reinforces the notion that disruptive behaviour disorders such as CD, ODD and ADHD may share a common aetiology in terms of neurobiological function.

## 1.6 Theoretical Context of Dysfunctions in Conduct Disorder With and Without Callous Unemotional Traits

One of the possible mechanisms through which conduct disorder problems emerge may be faulty self-regulation. Self-regulation is the 'effortful monitoring, evaluating, and, if need be, altering of behaviour' (Newman & Wallace, 1993). In their review Newman and Wallace propose that self-regulation requires the integration of a variety of motivational (e.g. affective or rewarding) and cognitive factors (e.g. attentional/cool executive functions). One of the most prominent theories of self-regulation is Gray's reinforcement sensitivity theory (Gray, 1987). Gray proposed three arousal systems; the Behavioural Activation System (BAS), Behavioural Inhibition System (BIS) and the Nonspecific Activation System (NAS). The BAS is proposed to be sensitive to reward, while the BIS is sensitive to punishment and both compete to increase NAS activity to override activity in the other system. CD problems may therefore arise as a consequence of an overactive BAS system and faulty BIS system. Literature reviewed in this chapter suggests that this notion would be valid; children and adolescents with CD problems

with and without CU traits make more risky decisions and show a preference for rewards despite being punished (Syngelaki *et al.,*2009; Luman *et al.,*2010), make perseverative errors when reward contingencies change from rewarding to punishing (Matthys *et al.,*2004), and show greater BOLD responses in neuroimaging tasks during the notification of reward (Bjork *et al.,*2010). Not only does the data reviewed in this chapter suggest that the CD group are more reward-oriented, but there is also evidence to suggest that the cool executive mechanisms through which the individuals execute these behaviours may also be dysfunctional. Evidence reviewed here suggests that children and adolescents with CD show working memory deficits (Syngelaki *et al.,*2009; Cauffman *et al.,*2005; Barnett *et al.,*2009) this could mean that they are less able to represent, or hold goals in mind meaning they become more driven by their immediate surroundings or by immediate gratifications such as rewards. This proposition would therefore mean that CD problems may arise as a consequence of an overactive reward system and failures in other domains of executive functions.

## 1.7 **Summary and Current Thesis Aims**

From the work summarised here it is clear that many advances have been made in the diagnostic refinement of the CD phenotype in terms of definition (e.g. E-O, A-O), sub-typing (with and without high CU traits), known risk factors (e.g. adverse environment) and adult outcomes (e.g. risk for substance misuse and mental ill health). There have also been great moves made toward refining the neurocognitive and neurobiological phenotype in terms of emotional reactivity and higher order executive function profiles. However there are still gaps in the literature which researchers must endeavour to address. Although there has been a substantial increase in the number of high quality studies investigating CD problems in females, such as the Pittsburgh Girls Study, there is still a dearth of experimental investigations (e.g. fMRI) of suitable statistical power to make meaningful comparisons between males and females with CD. This is understandable; neuroimaging is very expensive and many of the

existing studies would need to at least double in size in order to make between-group comparisons, increasing the average sample size from around 50 participants to 100. A recent research review by Moffitt and colleagues (2008) summarised some of the areas where research into CD problems is still lacking. The authors identified a number of research themes that included; (1) the utility of CU traits as a subtype for CD problems and the investigation of CU traits in typically developing individuals, (2) using neuroimaging phenotypes as biomarkers for the classification of CD problems, (3) CD symptom manifestation and associated difficulties in females (Moffitt *et al.,*2008).

This thesis aims to address some of these research themes through the investigation of the clinical, temperamental, neuropsychological and neurobiological profile of CD problems in a large representative community sample of European adolescents and explores domains of emotional reactivity and hot and cool executive function. In addition to investigating gender specific traits associated with CD, this thesis explored the extent to which CU traits allow the delineation of a sub-population of individuals who show a distinct neurofunctional and temperamental profile, compared to a comparable (average CU) peer group. Chapter Two describes the methodology used in this thesis including the overlap in symptoms between CD and ADHD and how this was addressed, the nature of working with data from a multi-site European study, a description of the study cohort and then method specific information including; clinical, personality, neuropsychological and neuroimaging methods used and the quality control procedures that were applied to all data. Chapter Three describes an investigation into the clinical, temperamental and behavioural profile of males and females with CD, with and without high CU traits, and explores the extent to which these groups are similar to one another. Chapter Four uses an emotional reactivity paradigm depicting emotional stimuli in order to investigate whether CD males and females differ at the neurobiological level from one another, and if CU may help to identify a subset of individuals

for whom emotional stimuli might result in a different pattern of neurofunctional reactivity altogether. Chapter Five uses tasks investigating cool executive function to explore the extent to which these abilities are impaired in males and females with CD. Cool EF was assessed using neuropsychological assessment of working memory and inhibitory control using a response inhibition fMRI paradigm. This chapter also investigates the extent to which these abilities are modulated by hyperactivity/inattention symptoms and verbal IQ. Finally, Chapter Six investigates hot EF using a neuropsychological gambling task to assess risk taking, and an fMRI paradigm investigating reward processing at different stages; anticipation of reward, receipt of reward and the omission of an expected reward. The extent to which males and females with CD are similar to each other in terms of neuropsychological and neurofunctional profile is explored, as is the contribution of CU traits.

# Chapter 2 Methodology

*This chapter describes the study population, neuropsychological, personality, clinical and neuroimaging methods used in this thesis. This chapter also addresses issues such as the overlap in aetiology between CD problems and other conditions such as ADHD symptoms, and documents how these will be addressed.*

## 2.1 The IMAGEN Study

***Background***

IMAGEN is a multi-site collaboration between eight European study centres. It is a multidisciplinary study using extensive behavioural, neuropsychological, functional and structural neuroimaging and genome-wide association analyses of 2000 14 year old adolescents. The aim of IMAGEN is to identify the genetic and neurobiological basis of individual variability in reinforcer sensitivity and emotional reactivity, and to determine the extent to which these characteristics are predictive for the development of neuropsychiatric disorders. As such, the adolescents were first assessed at 14 years old and then periodically followed up two years later at age 16 and then age 18. This thesis includes data collected at age 14 and 16. IMAGEN is led by Professor Gunter Schumann, and is funded by the European Community's Sixth Framework Programme (LSHM-CT-2007-037286). See Schumann *et al.,* (2010) for further information.

***Ethical Approval***

Each study site (Institute of Psychiatry, University of Nottingham, Trinity College Dublin, Charité University Berlin, University Medical Center Hamburg-Eppendorf, Central Institute of Mental Health Mannheim, Technical University Dresden (TUD) and the National Institute of Health and Medical Research (INSERM) Paris) sought local Ethical Approval for the project. A

central multidisciplinary ethics group was established to monitor issues and protocols related to consent, confidentiality, data protection and research involving a vulnerable group (adolescents). In addition the group was set up to design strategies for dealing with issues related to novel and incidental findings related to genetic, biological and environmental factors in personality and psychopathology.

***Participants and Recruitment***

As one of the aims of IMAGEN is to address the extent to which environmental and genetic factors affect brain and behaviour, the recruitment protocol was designed to limit ethnic heterogeneity through the preferential recruitment of adolescents with European ethnicity. Each site was encouraged to adopt a strategy that allowed for the recruitment of an ethnically homogenous sample, while maintaining diversity in terms of socioeconomic status, academic achievement, and behavioural functioning. As such, adolescents were recruited from mainstream state and independent schools and special schools for excluded children. Researchers visited schools and gave presentations about the project and distributed information packs to the adolescents to take home and show their parents. If the adolescent was interested in taking part they sent a 'statement of interest' slip to the study team. The study team then contacted the parent or guardian of the adolescent to discuss the study aims and inclusion/exclusion criteria for participation. If there were no contraindications for participation, the parent and adolescent sent written informed consent to the study team and took part in the assessments.

IMAGEN is a longitudinal study; at age 16 the participants were invited to participate in the project again. Participants who had indicated at age 14 (baseline) that they consented to be contacted for the next phase of the study were sent information sheets and informed consent

forms for follow up one (FU-1). This thesis uses data from both the baseline and FU-1 assessment.

***Exclusion Criteria***

Participants were excluded prior to assessment if they met any one of the following criteria; were unable to attend a full assessment day at the research institute, had contraindications for magnetic resonance imaging such as metal implants (pacemakers, aneurysm clips), non-correctable visual deficits, premature birth, neurological problems such as epilepsy, brain tumour, or head trauma, or were receiving treatment for illnesses such as schizophrenia or bipolar disorder.

***Assessment Protocol: Home***

Psytools software (Delosis Ltd, London, UK) was used to conduct the behavioural characterisation via its internet-based platform. The assessment battery of personality questionnaires and cognitive tasks was self-administered both in participants' homes and at the study centre and took approximately two hours to complete. The tasks were presented in a pseudo-randomised order to promote attentional focus and attempt to control for task order effects. Context checks were administered at the start of each task to identify whether the data were of good quality and included information regarding confidentiality of the situation i.e. was the adolescent alone; the noise level; their mood; time constraints and their tiredness. If any of the tasks were completed with dubious quality the participants were asked to re-complete the task at the study centre. The same automated platform was used for the FU1 assessment.

***Assessment Protocol: Institute***

Participants and their parent/guardian were invited to take part in an assessment at the study centre. Working with trained research staff the parent/guardian completed a computerised clinical assessment of their child's mental health, and also completed questionnaires about their own personality and the family environment. The adolescent completed the same computerised clinical assessment of their own mental health and also took part in neuropsychological assessments, a two hour structural and functional magnetic resonance imaging session, and gave a sample of their blood. To ensure all data were acquired consistently across sites regular training workshops were held during the baseline data collection phase, conducted by trained clinical psychologists and researchers.

## 2.2 Clinical, Personality and Neuropsychological Assessments

This section describes the specific measures used in this thesis and the various quality control procedures that were applied to the data. As the quality and consistency of the data varied from task-to-task this resulted in a varying number of participants for whom data could be analysed, therefore each empirical chapter provides a summary of the demographic variables such as IQ, age and gender at the beginning of each analysis section.

***Strengths and Difficulties Questionnaire***

Adolescents with CD problems were identified using the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). The SDQ is a well validated tool that indexes common behavioural difficulties in 3-16 year olds (Goodman & Scott, 1999; Goodman, Ford, Simmons, Gatward & Meltzer, 2000). It covers five domains; emotional problems (5 items), conduct problems (5 items), hyperactivity/inattention (5 items), peer relationship problems (5 items) and prosocial behaviour (5 items). Two versions were used in IMAGEN; parent-rated

(Goodman, 1997) and adolescent-rated using a developmentally appropriate version (suitable for 11-16 year olds; Goodman, Meltzer & Bailey, 1998). For internalising symptoms (emotional problems) adolescent rated symptom count scores were used and for externalising symptoms (conduct/hyperactivity-inattention/peer relationship problems) parent rated symptom count scores were used. This mixed informant method for symptom reporting was favoured as parents or guardians are thought to be better placed to accurately report directly observable behavioural symptoms while adolescent or child informants are better at reporting subjective symptoms (Herjanic & Reich, 1997).

The SDQ also contained an impact section which asked the respondent to declare if there is a problem and if there is, asks about the chronicity, distress, social impairment and whether the problem is a burden. This section is extremely helpful as it is used in combination with the symptom count scores to determine psychiatric 'caseness' (Goodman *et al.,*1998; Goodman, Renfrew & Mullick, 2000). The SDQ 'caseness' score results in one of three categories; unlikely, possible and probable. This thesis uses the case group likelihood to determine individuals who have sufficient CD problems as rated by both the adolescent and parent to result in them being classed as a possible or probable case. The possible and probable CD groups were merged together and are henceforth referred to as 'conduct disorder problems (CD)' and the unlikely group are referred to as 'controls'. See Appendix Chapter 2 for the SDQ items and calculations used to determine caseness. This thesis favoured the use of a dichotomous classification for CD and controls so that any significant findings could be discussed and interpreted in terms of existing research findings of CD clinical groups.

Both the adolescent and the parent/guardian completed the SDQ as part of the institute assessment at age 14 and then remotely at home at age 16. They were seated in a quiet private room with a researcher who introduced the task. The SDQ was administered through a

computer automated system designed by (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). Once the SDQ was complete the computer system moved seamlessly into a detailed clinical assessment which took up to an hour to complete (Development and Wellbeing Assessment; DAWBA).

***Wechsler Intelligence Scale for Children (WISC-IV)***

Five sub-tests of the WISC-IV were administered in the same order at all study sites; Block design, Similarities, Digit Span, Vocabulary and Matrix Reasoning. Block design measured abstract visual problem solving. Scores from the Similarities and Vocabulary sub-tests were combined and an index of Verbal IQ was calculated. Similarities measured the adolescent's ability to think abstractly and asked them to decide how two things (e.g. horse and dog) or two concepts (e.g. hope and fear) were alike. Scoring was dependent on the quality of response. The Vocabulary sub-test measured verbal fluency and knowledge of word meanings. The adolescent was required to explain what a word meant by defining or describing what it does. Scoring for this sub-test was also dependent on the quality of response. Scores from the Block Design and Matrix Reasoning sub-tests were combined and an index of Performance IQ calculated. Block design measured abstract visual problem solving. A pattern was shown to the adolescent that they recreated using white and red coloured blocks. Matrix Reasoning indexed fluid reasoning. The adolescent was shown a partially completed grid and was asked to select the item (from a choice of items) that properly completed the matrix.

The Digit Span subscale was divided into two tasks; digit span forwards and digit span backwards. Number sequences were read aloud to the participant at a rate of one digit per second. Both tasks began with an initial item of two digits and each item had two trials. The number of digits that needed to be recalled increased by one digit per item. On each forward

trial the participant was asked to recite the digits in the same order they were given. On the backwards trials the participant was required to recite the digits in reverse order to that which they were administered. For all WISC subtests the adolescents were seated in a quiet environment with a trained researcher and notices were displayed requesting they were not disturbed.

***Subscales from the Substance Use Risk Profile Scale (SURPS)***

The Substance Use Risk Profile Scale (SURPS) (Woicik, Stewart, Pihl, & Conrod, 2009) is a short index of four personality traits that are risk factors for the development of psychopathology including Hopelessness, Anxiety Sensitivity, Impulsivity and Sensation Seeking. The SURPS was completed during the home assessment using Psytools at age 14 and 16. The SURPS was included as a way of assessing temperamental variation in trait impulsivity which has been previously associated with behavioural disinhibition and CD problems. An additional subscale was also included, Hopelessness, to investigate variation in a trait associated with the development of internalising symptoms such as depression. While these scales are perhaps suboptimal, for instance impulsivity would have been potentially better assessed by a more widely used measure such as the Barratt Impulsivity Scale, this study was limited to those tools that had been agreed by the IMAGEN consortium members. A copy of the subscales used in this thesis (Hopelessness and Impulsivity) and scoring may be found in Appendix Chapter 2.

***Subscales from the NEO-PI-R***

Five broad dimensions of personality based on the Five-Factor model of personality (McCrae & John, 1992) were measured using the NEO-PI-R (McCrae, Costa Jr, & Martin, 2005); agreeableness, conscientiousness, neuroticism, extraversion and openness. The NEO was completed by the adolescent during the home assessment using Psytools at age 14 and 16.

Subscales from the NEO were included as a comparison measure of temperamental variability over time. The NEO is one of the widest used personality indices across Europe and as such was considered a good marker for test-retest reliability, and was used as the 'Gold Standard' measure to compare the temporal stability of the locally developed CU trait scale against. A copy of the subscales may be found in Appendix Chapter 2.

***Interpersonal Reactivity Index***

The Interpersonal Reactivity Index (IRI) (Davis, 1980 & Davis, 1983), was included to investigate the relationship between the study-developed CU trait scale and a validated measure of dispositional empathy and related constructs. The IRI was administered to the adolescents as part of the online IMAGEN battery at age 16, but not age 14. It was included to assess the extent to which the locally developed measure of CU traits could be used to infer some of the associated traits it was intending to measure such as a lack of empathy. It was hypothesised that if the CU trait scale at age 16 was negatively associated with the Empathic Concern subscale at age 16 then the scale was capturing some of the same trait and would then be considered a useful measure at age 14 in the absence of the ideal measure. The IRI includes four subscales; Perspective Taking (PT; adopting another person's point of view), Empathic Concern (EC; experiencing feelings of sympathy and compassion for others), Personal Distress (PD; experiencing distress in response to other people's distress) and Fantasy Scale (FS; putting oneself into fictional situations). The IRI measure at age 16 was also useful to tap emotional reactivity in the participants, using the personal distress scale, and also to investigate perspective taking ability using the PT scale. The Fantasy Scale was not analysed. A copy of the IRI items and their scoring key can be located in Appendix Chapter 2.

***Callous Unemotional Traits***

While the IMAGEN battery is comprehensive it did not contain a standard measure of callous unemotional traits. Previous work suggested it was possible to create a proxy tool for inferring CU traits by combining items from other standardised measures. Dadds and colleagues (2005) investigated the factor structure of one of the most commonly used measures of antisocial behaviour in children suitable for use in community samples, that contains a measure of CU traits; the Antisocial Process Screening Device (APSD) (Frick & Hare, 2002). The researchers found items from the Strengths and Difficulties Questionnaire Prosocial Scale loaded significantly with items from the APSD-Callous Unemotional (CU) scale. The APSD-CU items were; 'unconcerned regarding others feelings', 'no guilt' and 'breaks promises' and the items of the SDQ Prosocial Scale were; 'inconsiderate of other people's feelings', 'does not share with other children', 'unhelpful if someone is hurt, upset or feeling ill', 'not kind to younger children' and 'does not volunteer to help others'. The authors asserted that this factor reflected the child's propensity to be uncaring towards others and termed this factor CU (Dadds, Fraser, Frost, & Hawes, 2005). Guided by these findings items were selected from standardised measures in the IMAGEN battery and their factor structure examined.

Four items were selected from the SDQ Prosocial Scale (Goodman, 1997); '*I am helpful if someone is hurt, upset or feeling ill*', '*I try to be nice to other people, I care about their feelings*', '*I am kind to younger children*' and '*I often volunteer to help others*' and were reverse scored. The item that pertained to sharing with other children was omitted as it showed the weakest loading in investigation of Dadds *et al.,*(2005) (.49). In addition, two items were drawn from the NEO-PI-R Personality Scale (McCrae & John, 1992; McCrae, Costa & Martin, 2005) that were deemed to reflect the cold interpersonal style of individuals with CU; '*Some people think of me as cold and calculating*' and '*Some people think of me as selfish and egotistical*', both items were scored so that a high score reflected a higher CU trait and all items were self-rated.

Ideally a parent-rated measure would have been used, however as two items were selected from the self-rated NEO-PI-R, in order for the construct to meaningful in terms of the *type* of items included, a self-rated measure was accepted.

A confirmatory factor analysis showed the items sufficiently loaded with one another (all loadings were greater than 0.4, as per the Dadds *et al.,*investigation). The loading scores are shown on Table 2. The overall scale alpha (a measure of internal reliability) was moderate (0.62) but acceptable given the items were selected based on similarity to those used by Dadds *et al.,*(2005). Table 2 also shows that should any item be removed the internal validity of the scale would be degraded; therefore the six-item scale was accepted as a proxy self-rated measure of CU.

Table 2 CU Proxy Scale Factor Loading and Item Reliability

| **Item** | **Loading** | **Cronbach's Alpha if item deleted** |
|---|---|---|
| Some people think of me as cold and calculating | .52 | .60 |
| Some people think of me as selfish and egotistical | .54 | .59 |
| I am helpful if someone is hurt, upset or feeling ill | .66 | .56 |
| I try to be nice to other people, I care about their feelings | .67 | .56 |
| I am kind to younger children | .61 | .58 |
| I often volunteer to help others | .53 | .60 |

Table 3 shows a comparison between the CU Proxy Scale and two validated CU subscales from the clinical Psychopathy Checklist Youth Version (PCL-YV) and the Antisocial Process Screening Device (APSD). The items highlighted in blue text are those that were found to significantly load together according to Dadds *et al.,*(2005).

Table 3 Item Comparison Validated Instruments (PCL-YV and APSD) Compared to CU Proxy Scale

| PCL-YV | APSD | CU Proxy |
|---|---|---|
| Lack of remorse | No guilt | Some people think of me as cold and calculating |
| Shallow affect | Not motivated in structured activities | Some people think of me as selfish or egotistical |
| Callous, lacks empathy | Unconcerned regarding others feelings | I try to be nice to other people, I care about their feelings |
| Impression management | Does not show feelings | I am helpful if someone is hurt, upset or feeling ill |
| Manipulation for personal gain | Loses friends | I am kind to younger children |
| Failure to accept responsibility | Breaks promises | I often volunteer to help others (parents, teachers, children) |
| Grandiose sense of self worth | | |
| Pathological lying | | |

APSD Antisocial Process Screening Device, (Frick & Hare, 2001) 20-item measure of antisocial behaviour in children, suitable for use with community samples

PCL-YV Psychopathy Checklist Youth Version (Forth, Kosson & Hare, 2003) typically used with clinical/incarcerated population

Adolescents were classed as 'High CU' if they scored more than one standard deviation above the mean (a score of 7 or more; scale range 0-13). The reasons for setting this threshold are twofold. First, IMAGEN is a community sample and therefore scores are unlikely to be abnormally high. Second, this lenient threshold meant that sample sizes remained sufficiently

large in order to make meaningful between-group comparisons. The study sample was insufficiently powered to assess Low (versus average) CU traits in addition to High, especially in terms of overlap with CD case scores. Therefore, all other participants are those who scored fewer than 7 points on the CU scale, and are classed in the 'average' range for the present study sample.

***Test-Retest and Construct Reliability of the CU Trait***

Across time points from age 14 to age 16 data were available from 1131 individuals. The new CU scale showed a correlation coefficient of $r = .50$, which was highly significant ($p<.001$) and was comparable to the correlation across time points of the NEO (e.g. Neuroticism $r = .56$; agreeableness $r = .59$). The CU scores correlated slightly, but not significantly higher in males (N = 547, $r = .52$) than in females (N = 584 $r = .47$). As those individuals classed as 'High' CU were of particular interest the extent to which the 'High' group (scores ≥7 points) remained the same over time was also investigated. Of the whole group (N = 1131) individuals, 39 (6%) who had High CU at age 14 remained in this group at age 16, 50 (7%) adolescents who had Average CU at age 14 had developed High CU by age 16, while 65 (9%) who had High CU at age 14 had Average CU by age 16. See Table 4 for a breakdown of these figures by gender.

Table 4 CU Trait Stability Age 14 and Age 16

| | **Males N (%)** | **Females N (%)** |
|---|---|---|
| **Average CU Age 14 and Age 16** | 218 (69%) | 340 (86%) |
| **Average CU Age 14, High CU Age 16** | 27 (8%) | 23 (6%) |
| **High CU Age 14, Average CU Age 16** | 40 (13%) | 25 (6%) |
| **High CU Age 14, High CU Age 16** | 32 (10%) | 7 (2%) |

The association between CU and a measure of dispositional empathy; experiencing feelings of sympathy and compassion for others (Interpersonal Reactivity Index; IRI, Empathic Concern subscale) was also examined. It was expected that CU would correlate negatively with empathic concern. Correlation analysis of CU at age 16 (note: IRI only administered at age 16) showed a significant negative association between CU and Empathic Concern of $r$ = -.38, which was highly significant ($p$<0.001). The CU and EC scores correlated slightly, but not significantly higher in males (N = 357, $r$ = -.40, $p$<0.001) than in females (N = 434, $r$ = -.35, $p$<0.001). This suggested that while there was some degree of relatedness between the two constructs the proxy CU scale was perhaps not solely testing for a lack of empathy, although this would need to be confirmed with a standardised tool to confirm this supposition. The locally developed scale had good test-retest reliability, and performed comparably well to the NEO personality index. It has also been shown that NEO personality traits (McCrae, Martin, & Costa, 2005), which are widely measured and considered to be core personality constructs, vary over development and do not stabilise until adulthood, therefore one would not expect the correlation coefficient to be more than moderately associated.

***Cambridge Neuropsychological Test Automated Battery***

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was included to assess different aspects of executive function. The IMAGEN-specific tasks were always administered in the same order across all sites to ensure consistency. The order was as follows; Pattern Recognition Memory (Immediate recall; not investigated in this thesis), Affective Go/No-Go (not investigated in this thesis), Spatial Working Memory, Pattern Recognition Memory (Delayed recall; not investigated in this thesis), Cambridge Gambling Task and Rapid Visual Processing (not investigated in this thesis). Only spatial working memory and the Cambridge gambling task were investigated as they represented well-validated tasks through which to

replicate findings of other research groups of cool and hot executive dysfunctions in adolescents with CD problems.

*Spatial Working Memory*

The task tests how well participants are able to hold spatial locations and manipulate remembered items in working memory. A number of coloured squares are shown on the screen, and the aim of the task is to find 'blue tokens' that have been hidden inside the squares (referred to as boxes) by touching the screen. A demonstration is given by the researcher and then the participant is given three trials to practise the task. Task difficulty increases as the task progresses; from four boxes and four tokens to find, to six and then eight. The colour and position of the boxes changes from one trial to the next. The task takes approximately eight minutes to complete.

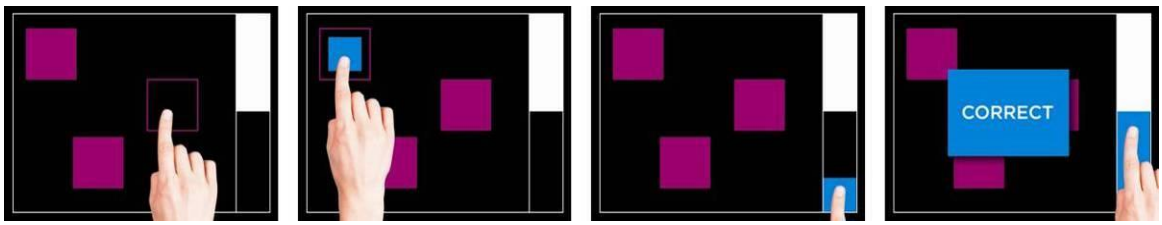


Figure 1 Schema of the CANTAB Spatial Working Memory Task

*Cambridge Gambling Task*

This task measures risk taking and decision making. A row of ten boxes is displayed across the top of the screen, some red and some blue. The participants are told that the computer has hidden a token inside one of the red/blue boxes and they need to decide which colour box it is in. The participant makes their choice by selecting the word red or blue at the bottom of the screen and then makes a wager in points, to reflect their confidence in this judgement. A

stake box displays the current wager which either increases or decreases as the participant waits. If the participant picks the correct coloured box then the wager amount is added to their points total, if they were incorrect then the wager is deducted from their total. The participants are instructed to try and accumulate as many points as they can.

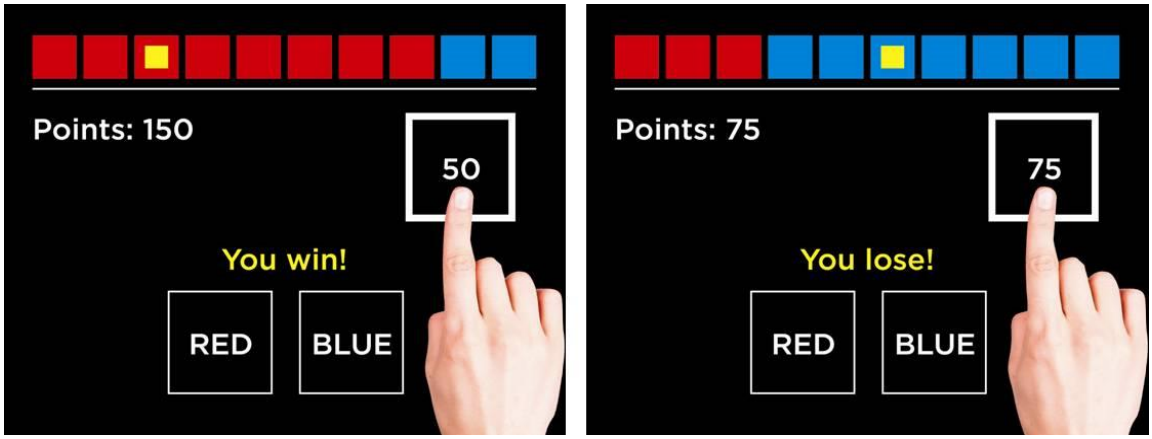


Figure 2 Schema of the CANTAB Gambling Task

*CANTAB Procedure*

Participants were seated in a quiet environment with a researcher and notices were displayed requesting they were not disturbed. The participant was seated directly in front of the screen (approximately 30-35cm distance between them and the screen) so they were able to comfortably reach the screen to touch it, while remaining with their back upright against a chair so they did not need to lean forward. The participants were instructed to use their dominant hand to touch the screen and were not given access to the keyboard or mouse. Participants were instructed to touch the screen to make their responses for the following tasks; Pattern Recognition Memory Immediate and Delayed Recall, Spatial Working Memory, and Cambridge Gambling Task, and were taught to respond using the press pad for the following tasks; Affective Go/No-Go and Rapid Visual Processing. For tasks where the researcher demonstrated steps (Spatial Working Memory & Cambridge Gambling Task) the

screen was arranged so that the researcher could reach it to demonstrate the test according to the instructions stipulated in the CANTAB manual, see Figure 3.

Figure 3 Researcher Demonstrating the CANTAB Spatial Working Memory Task (Left) and Participant Completing the Spatial Working Memory Task (Right)

The keyboard, mouse, and press pad were situated to the side of the computer, on the same side as the researcher. During tasks that required responses using the press pad (Affective Go/No-Go, Rapid Visual Processing), the press pad was moved to the front of the screen and arranged so that the response button was approximately 15 cm from the screen, see Figure 3. The researcher sat next to the participant and gave verbal instructions for each test, and specific verbal prompts and encouragements were used as stipulated by the CANTAB manual.

***Quality Control and Data Reliability***

All institute assessment task data were given a rating during the assessment. Data were rated as good, doubtful or bad by the researcher dependent on how well the assessment had been completed by the participant. An example of bad data was 'Participant's first language was not English/French/German'. This particular comment would mean that any WISC data that had been acquired would have to be excluded from analysis as the WISC must be conducted in the mother tongue of the participant. The assessment of a participant whose first language was

not the mother tongue of the country of assessment was rare, but did occur in a small number of cases. In the interests of treating all participants equally, adolescents and their families were invited to take part in the study if they indicated an express interest regardless of their language status. Doubtful data were those where the participant might not have concentrated fully on the task. The researchers recorded any comments they had about the integrity of the data. All comments and reliability ratings are available to consortia members when they download data from the IMAGEN project website. This project only works with data that were rated as 'Good' by researchers and had no unchecked performance flags from the Psytools home assessment tasks. Additional quality control procedures concerning the reliability of the neuroimaging data are discussed in the following sections.

## 2.3 Neuroimaging Acquisition and Analysis

***What is Functional Magnetic Resonance Imaging and what does it measure?***

Functional magnetic resonance imaging (fMRI) is a non-invasive way for researchers to investigate how the brain responds to different stimuli. The most common way to investigate neural activity is through Blood Oxygen Level Dependent (BOLD) imaging. This method makes the most of the fact that oxygenated and deoxygenated blood has different magnetic properties. The approach assumes that when different brain regions are active, for example neurons in the visual cortex fire in response to light, they require more oxygen, and so regional increases of oxygen rich blood are channelled to that area. fMRI does not measure neural response directly, rather it measures this 'hemodynamic response'. As the purpose of this approach is to detect a change in the signal, inferred by a change in regional blood flow, this means that two conditions need to be included. For example, if a researcher wanted to know which regions of the brain might be more exclusively involved in face perception, then they would subtract the activity of all the brain regions that are 'active' when the person views non-face objects. This should, in theory, leave only areas that are important for processing faces.

Similarly, if a researcher wanted to know all of the regions involved in visually analysing a face then they would compare that pattern of activation to that of activation during a baseline condition, such as a fixation cross.

There were two neuroimaging acquisition sessions in IMAGEN, each lasting 60 minutes. The emotional reactivity paradigm was a passive task (requiring no response from the participant), lasted for 5 minutes, and was administered in the first session. The Stop Signal Task (SST) was administered after the emotional reactivity task and lasted for 16 minutes. The Monetary Incentive Delay (MID) task was administered in the second imaging session and lasted for 11 minutes. Each participant took part in a demonstration session to familiarise them with the scanning environment and were shown an example of the task stimuli so they knew what to expect during the scanning session. The participants were given time to practise the SST and MID tasks on a laptop and each session lasted for around 3 minutes. Instructions for each task may be found in Appendix Chapter 2.

***Emotional Reactivity Task***

This task was adapted from Grosbras and Paus (2006). Participants watched 18-second blocks of either a face movie (depicting anger or ambiguity) or a control stimulus. Each face movie showed black and white video clips (200-500ms) of male or female faces. 5 blocks each of angry and ambiguous expressions were interleaved with 9 blocks of the control stimulus. Each block contained 8 trials of 6 face identities (3 female). The same identities were used for the angry and ambiguous blocks. The control stimuli were black and white concentric circles expanding and contracting at various speeds that roughly matched the contrast and motion characteristics of the face clips.

The ambiguous blocks contained emotional expressions that were classed as neutral (e.g. nose twitching); however previous research has suggested that neutral stimuli are not always interpreted as such. Functional imaging studies have found significant activation of the amygdala in response to the presentation of neutral faces in healthy adult males (McClure *et al.,*2004), in a clinical group of social anxiety patients and their matched control participants (Cooney, Atlas, Joormann, Eugene, & Gotlib, 2006), in adolescents with conduct disorder problems (Passamonti *et al.,*2010) and in young men who show significant violent behaviour (Pardini & Phillips, 2010). Taken together these studies suggest that neutral faces might be regarded as emotionally ambiguous and are referred to as such in this thesis. This study focused specifically on the effects of viewing angry faces on brain function so that any significant between group differences could be interpreted as a consequence of viewing unambiguous negative stimuli (anger).

The contrast examined in Chapter Four of this thesis was 'Angry vs. Control'. This was calculated by averaging together all the trials during which an angry face was displayed and all the trials during which the concentric circles were shown. The effects of the moving circles were then subtracted (removing the effects of viewing motion) leaving the remaining brain activation associated with specifically viewing an angry face. See Figure 4 for a schema of the task.

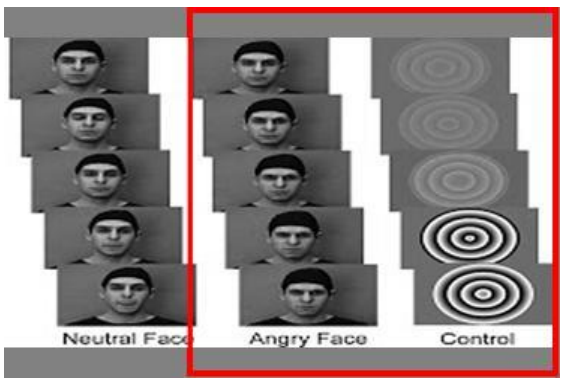

Figure 4 Schema of the Emotional Reactivity Task Stimuli: Angry and Ambiguous Faces and Control Stimuli

***Stop Signal Task***

This event-related task was adapted from Rubia, Smith, Brammer, Toone, and Taylor (2005) and Rubia, Smith, Taylor, and Brammer (2007). The participants were required to respond to visual go stimuli (go trials arrows pointing left/right; 83% N = 400) by pressing a button with either their left or right index finger corresponding to the direction of the arrow. The participants were instructed to withhold their response to the go stimulus when it was followed by a stop signal (stop trials, 17% N = 80), which was an arrow pointing upwards. Task difficulty was manipulated across the trials by varying the delay between the onset of the go arrow and the stop arrow using a tracking algorithm as described in (Rubia *et al.,*2005 and Rubia *et al.,*2007). The tracking algorithm altered the time between the go-stimulus and stop-stimulus onsets as a function of the participant's performance on previous trials. The algorithm ensured that the participants were successful on 50% of stop trials so that they worked at their own maximum capacity. Stimulus duration in the go trials was 1000ms, and varied between 0-900ms in stop trials by 50ms steps. This thesis analysed the contrast 'stop success'; which was calculated by averaging together all the trials of each participant where they successfully inhibited their response to the stop signal. This contrast was chosen as Chapter 5 of this thesis is concerned with the investigation of cool executive function processes including response inhibition. This contrast was included so that activation of the neural structures involved in response inhibition would be most clearly defined. In addition this task recorded the reaction time of the responses; the mean stop signal delay (average time between the go and the stop signal) from the mean reaction time to go trials. See Figure 5 for a schema of the task.

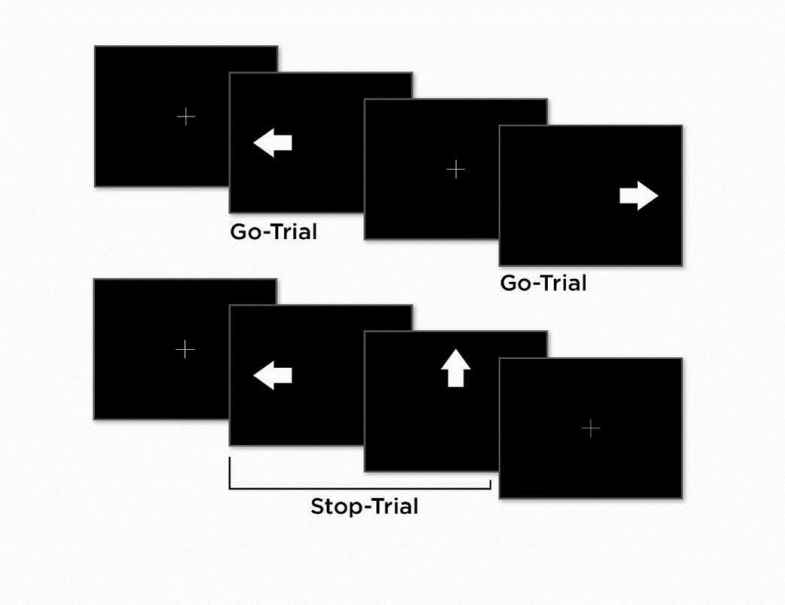


Figure 5 Schema of the Stop Signal Task

***Monetary Incentive Delay Task***

Initially developed by Knutson, Westdorp, Kaiser, and Hommer (2000) this event-related task is designed so that both reward anticipation and reward outcome may be modelled. In each trial (N = 66, 10 second duration) one of three cues appeared on the left or the right of the screen. A triangle was worth zero points, a circle with one line through it was worth two points and a circle with three lines through it was worth ten points. The shape informed the subject which side of the screen the target shape (a white square) would subsequently appear, and how many points they could earn on that trial. The participants were instructed not to respond until the white square appeared and were told to respond using their left or right index finger depending on which side of the screen the white square appeared. Immediate feedback was given to the participants regarding their success or failure and the points total increased or stayed the same according to their performance. A tracking algorithm ensured that task difficulty (target display duration varied between 250-400ms) was adjusted so that each participant had success 66% of the time.

This task was incentivised using chocolate sweets rather than the country's currency due to the age of the participants. This thesis used three contrasts for analysis; (i) anticipation of large win vs. anticipation of no win, outcome; (ii) feedback large win vs. no win and (iii) feedback missed large win vs. feedback no win. See Figure 6 for the task schema. The first contrast took an average of all trials where the participant anticipated a large win as this should elicit the largest response from the brain regions involved in reward processing, and subtracted the average of all trials where the participant was not expecting to win. In theory this then leaves those areas of brain preferentially active when anticipating a large win. The second contrast took an average of all those trials where the participant was given feedback that they had won the largest number of points and removed an average of those trials where they were given feedback that they had not received any points (when they were not expecting to win), leaving all those brain regions preferentially active in response to receiving a reward. The final contrast averaged all of those trials where the participant was given notification they had failed to gain the largest reward and subtracted an average of the trials where they were given feedback that they had not won any points. The study used the maximally rewarding and unrewarding conditions to elicit maximum brain activation to ensure activations were associated only with reward processing.

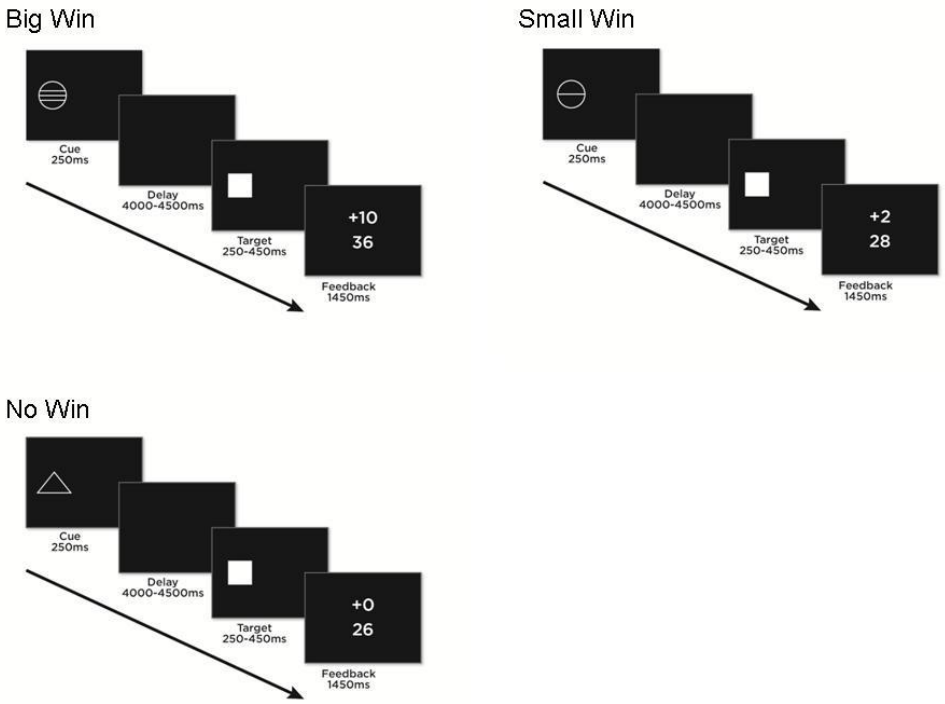


Figure 6 Schema of the Monetary Incentive Delay Task

***Neuroimaging Acquisition and Analysis***

Structural and functional MRI data were acquired across all IMAGEN centres with 3-Tesla MRI scanners of different manufacturers (Siemens, Philips, General Electric & Bruker). Standardised equipment was used at all sites for the visual and auditory presentation (Nordic Neurolabs; NNL) including a pair of goggles that were adjusted to each participant's visual acuity and a pair of response grips. All sites used the same scanning protocol; high-resolution T1-weighted 3D structural images were acquired for anatomical localisation and registration with the functional time series. Blood oxygen-level dependent (BOLD) functional images were acquired with a gradient-echo, echo-planar imaging (EPI) sequence. The number of volumes collected per subject varied by task; for the emotional reactivity task 160 volumes were acquired, the MID collected 300 and the SST collected 444. Each volume contained 40 slices (2.4mm slice thickness, 1mm gap) aligned to the anterior commission/posterior commission line. The echo-time was optimised (TE 30ms; TR 2200ms) to reliably image subcortical regions.

***First Level Analysis***

The IMAGEN fMRI data were pre-processed centrally by Biostatistics specialists at Neurospin in Paris using SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/). At the first level of analysis BOLD-response changes for each participant were assessed for each experimental condition of each task. The functional images were corrected for movement (realigned to the first volume), slice timing, non-linear warping of each EPI to a custom EPI template and were smoothed with a 5mm full-width half maximum gaussian filter. Estimated movement parameters were added to each design matrix in the form of 18 additional columns (3 translations, 3 rotations, 3 quadratic and 3 cubic translations, and each 3 translations with a shift of ±1 TR). Statistical parametric maps from each individual were then taken to the second-level analysis. Please see Appendix Chapter 2 for the first level model design matrices that were used by the team at Neurospin.

***Quality Control and Data Reliability***

In addition to the exclusion criteria presented on page 46, imaging data were removed from further analysis after pre-processing if they met any of the following criteria; if anatomical abnormalities were detected, if the participant reported problems during the functional imaging tasks e.g. falling asleep or difficulty seeing the task stimuli, or if they showed outlying activation values across voxels in the particular contrast under investigation (outlying values calculated by Virgile Fritsch, a Biostatistician at Neurospin).

## 2.4 Analysis Consideration: Overlap in aetiology between Conduct Disorder and Attention Deficit Hyperactivity Disorder

Conduct Disorder (CD) and Attention Deficit Hyperactivity Disorder (ADHD) are grouped together in the DSM-IV as both are associated with significant disruptive behaviour. CD problems include aggression toward people and animals, the destruction of property, deceitfulness or theft and a serious violation of rules, while ADHD behaviours include restlessness and over activity, difficulty concentrating, poor attention span and not thinking before acting. Studies have found that there can be substantial overlap or co-morbidity between CD and ADHD disorders in clinical (Biederman *et al.,*2006) and community samples (van Lier, Verhulst, van der Ende, & Crijnen, 2003; Waschbusch, 2002). This overlap indicates that these disorders have a shared aetiology, at least to some extent. When disorders appear to have a shared aetiology there are some important implications for the researcher to consider. An overlap in symptom dimension makes it more difficult to refine the phenotype of interest. Some of the research reviewed in Chapter 1 grouped participants together on the basis of diagnosis. This meant the authors were able to address the issue of shared aetiology to an extent e.g. by having a separate ADHD/CD group to compare to the CD only and Control groups, e.g. Schoemaker *et al*. (2012), Barnett *et al*. (2009), Clark, Prior, and Kinsella (2000). This approach has many advantages however it has not been commonly applied across research studies. Consequently this poses challenges when researchers attempt to make advances in the refinement of the cognitive and neurobiological phenotype underlying conduct disorder problems if one does not adequately account for above average levels of ADHD symptoms. This thesis attempts to address the issue of co-occurring symptoms of hyperactivity/inattention in these studies by controlling for this symptom dimension where appropriate, especially during the analyses of tasks where deficits linked to ADHD symptoms (e.g. executive function tasks) have been shown.

# Chapter 3 Characterising Conduct Disorder Problems and Callous-Unemotional traits in the IMAGEN Sample; effects of Gender and Callous Unemotional traits

## 3.1 Introduction

The exploration of gender differences in the clinical symptom manifestation of individuals with conduct disorder is complicated by variation in the methodology, sampling and measurements used by researchers. This chapter describes a study investigating clinically relevant symptoms, personality traits and empathy and perspective taking abilities in adolescents with and without conduct disorder problems, and explores the extent to which these symptoms and traits further vary as a function of both callous-unemotional traits and gender.

### *The Clinical Profile of Males and Females with Conduct Disorder Problems*

The issue of gender differences in conduct disorder problems was discussed in the introduction in section 1.2, with particular attention to the similarities in developmental trajectory. In terms of clinical symptom profile there is some evidence to suggest that the comorbid clinical symptom profile of males and females with CD problems might be different, although the findings are mixed. The most commonly reported symptoms that co-occur with CD are externalising (ADHD) problems, both in clinical (Biederman *et al.,*2006) and community samples (van Lier *et al.,*2003; Waschbusch, 2002). There is some evidence to suggest that when males and females have both hyperactive/inattentive and CD problems, females may be worse off compared to males in terms of IQ, peer relationship difficulties and CD symptoms (Waschbusch, 2002). However some studies did not find any effect of gender (van Lier *et al.,*2003) making it difficult to form concrete assertions about the extent to which females are afflicted by comorbid externalising symptoms.

There is evidence to suggest that females and males differ in terms of co-occurring internalising problems, although again the findings are mixed. Polier *et al.,*(2012) found that in a community sample, internalising problems (depression and anxiety) were more common in females compared to males, however Maughan *et al.,*(2004) found that males and females with conduct disorder or oppositional defiant disorder were equally affected by comorbid symptoms of depression and anxiety.

In addition to differences in the rates of clinical symptoms in males and females with CD, there is evidence for temperamental variation. Despite finding that CD girls showed significantly fewer non-aggressive CD problems (lying, stealing and destruction of property) compared to males, they did not differ significantly from males in terms of overall CD symptom count and aggressive symptoms (Maughan *et al.,*2004). There is also some evidence for gender differences in temperamental risk factors associated with developing CD. In males hyperactivity, hyperactivity plus unhelpfulness, and hyperactivity plus unhelpfulness and a fearless temperament were all associated with a greater risk for developing CD problems, while only hyperactivity and unhelpfulness together conferred a greater risk for CD problems in girls (Cote *et al.,*2002).

It is possible that one of the reasons why researchers are unable to make clear-cut inferences regarding the clinical profile of CD males and females is due to the confounding influence of callous unemotional traits. This is discussed in the next section.

***Conduct Disorder in Males and Females and the Influence of Callous Unemotional/Psychopathic Traits***

*Clinical and Temperamental Symptoms*

A very recent study has investigated gender-specific patterns of clinical symptoms as a function of CU traits. Pechorro and colleagues found that, on average, incarcerated females showed lower CU trait scores and higher emotional symptoms than males, but showed no difference in CD symptom severity (Pechorro *et al.,*2013). Essau and colleagues (2006) have also presented evidence for gender-specificity in clinical symptom measures. They found that self-rated CU was associated with internalising symptoms, and was more strongly associated with conduct problems and antisocial behaviour in females than in males. In terms of personality traits they found that callousness was significantly associated with disinhibition, sensation seeking, and a lack of conscientiousness in females ($r > 0.3$), while in males the callous dimension was much less associated with these measures (Essau, Sasagawa, & Frick, 2006). This evidence suggests that when females are affected by both conduct and CU problems they show a more diverse constellation of temperamental and clinically relevant symptom problems than males.

*Aggressive Behaviour*

There is evidence to suggest that callous unemotional/psychopathic traits may also exacerbate aggressive behaviours. Penney and Moretti (2007) found that high trait psychopathy (measured using the Psychopathy Checklist-Youth Version; PCL-YV) was associated with overt aggression, more acts of relational aggression, an increased likelihood to be aggressive towards a peer, and more violent and non-violent offenses in a clinical sample of both males and females (age 12-16). These effects were similar in a community sample, although here they were gender-specific; Marsee *et al.* (2005) found that self-reported psychopathic traits

(Antisocial Process Screening Device; APSD) were more strongly associated with overt-aggression in males than in females.

A recent study has examined the extent to which CU and CD problems can also be used to determine bullying behaviour. Viding and colleagues (2009) found that CU traits were associated with higher levels of direct bullying (face-to-face verbal/physical), and that CU traits increased the risk for indirect bullying (subtle/covert) when the individual also had conduct problems. Males were more likely to be labelled direct bullies while females were more likely to be indirect bullies and conduct problems were more strongly related to direct bullying in females (Viding, Simmonds, Petrides, & Frederickson, 2009). An important question to address is why individuals with conduct problems and CU traits are more likely than those with CD alone to bully others. Researchers have suggested that a lack of empathy might be one of the underlying causes and this is discussed in the next section.

***Empathy and Perspective Taking***

A growing body of evidence has emerged documenting the extent to which individuals with CD problems/antisocial behaviour who also have high CU/Psychopathic traits, might have difficulties with empathy and perspective taking ability. A study by Jones and colleagues (2010) found that male children and adolescents (aged 9-16) who had both CD problems and high psychopathic traits showed empathy deficits; this group cared less about being punished for their actions and cared less about the feelings of victims of aggression than control participants (Jones, Happe, Gilbert, Burnett, & Viding, 2010). The authors found that this group showed no impairment in Theory of Mind ability, that is, the ability to attribute and infer the thoughts and intentions of others (Premack & Woodruff, 1978). Reduced empathy in CD plus CU was also demonstrated by Pardini and Byrd (2012) in that high CU was associated with a

lack of concern regarding punishment and caring relatively little about victim suffering. Both research groups found that high psychopathic/CU traits were associated with a domineering style; Jones *et al.,*(2010) found that the conduct problem plus high psychopathic trait group placed value on being in control of a situation, and Pardini and Byrd (2012) found that high CU traits were associated with a view that aggression was a means to dominate others.

Similar effects have also been found in a community sample; trait psychopathy was associated with lower affective empathy in a cohort of undergraduates (Mullins-Nelson, 2006). While in a clinical sample of incarcerated male offenders, researchers found that high psychopathic traits were associated with a lack of compassion (Domes, Hollerbach, Vohs, Mokros, & Habermeyer, 2013), and impaired empathic understanding in ASPD males with high trait psychopathy (Dolan & Fullam, 2004).

The research summarised here suggests that conduct disorder problems, callous unemotional traits and gender might all interact to result in a complex clinical and temperamental profile, although this evidence is not without limitation. Very little research has been conducted that makes direct comparisons between males and females, and where gender differences have been investigated the extent to which CU/Psychopathic traits might affect findings has not always been considered.

***Summary and Study Aims***

This study was concerned with refining the clinical, temperamental and behavioural profile of males and females with CD, and explores the extent to which CU traits allow for the identification of a sub-group of individuals, who show a different profile to those with CD problems only. This approach also accommodates the characterisation of a group for whom CD

problems are absent, but who might show temperamental and/or clinical and behavioural traits that are different to their unaffected peers (controls).

This study investigated temperamental and clinical variables at age 14; externalising clinical symptoms (Hyperactivity/Inattention and Peer Relationship Difficulties) and an externalising temperamental variable (Impulsivity), and internalising clinical symptoms (Emotional Problems) and an internalising temperamental variable (Hopelessness). It was predicted that CD would be associated with increased hyperactivity/inattention, emotional symptoms and peer relationship problems compared to controls, and there would be two gender effects; (i) CD in females would be associated with more emotional symptoms compared to males with CD and (ii) CD males would experience more hyperactive/inattention symptoms than CD females. The extent to which CU interacted with both CD and gender was explored. In terms of personality variables it was predicted that CD adolescents would score higher for trait impulsivity and hopelessness scores compared to controls. This effect was also predicted to be gender specific; females with CD were predicted to show greater hopelessness scores compared to males with CD. In terms of CU it was predicted that high CU would be associated with higher trait impulsivity in CD groups.

At age 16 dispositional empathy (the tendency to experience sympathy and concern towards others), perspective taking (adopting the psychological perspective of others), and personal distress (the experience of distress in response to distress in others) were investigated. Overall it was predicted that females would rate themselves as more empathic than males, and that control participants would rate themselves as more empathic than the CD group. It was predicted that CU would moderate empathic concern in both the control and CD group, specifically, high CU would be associated with lower empathic concern scores and this would be exacerbated in the CD group with high CU. It was predicted that overall females would

report more personal distress than males, as would the control group, in comparison to the CD group. Additionally it was predicted that CU would be associated with lower levels of personal distress. The extent to which CU, CD and gender interacted in terms of personal distress was explored. Finally, it was predicted that there would be no main effect for perspective taking ability; neither would there be any significant interactions in terms of gender or CU.

## 3.2 **Method**

***Participants***

As described in Chapter 2, section 2.2, participants with Conduct disorder problems (CD) were identified as those who were classed as 'possible' or 'probable' CD cases (N = 281) according to the Strengths and Difficulties Questionnaire (SDQ). All participants who were classed as 'unlikely' to develop CD were classed as Controls (N = 1262).

***Materials and Procedures***

*Standardised Assessment Tools*

This study used symptom count scores from the SDQ (Goodman, 1997); Hyperactivity/Inattention, Peer Relationship Problems and Emotional Symptoms. Personality trait scores of Impulsivity and Hopelessness were used from the Substance Use Risk Profile Scale (SURPS; Woicik *et al.,*2009). The Interpersonal Reactivity Index (IRI; Davis, 1980 & Davis, 1983) was included at age 16 and was used to assess between-group differences in perspective taking, personal distress and empathic concern.

*Study Developed Tool: Callous Unemotional Traits.*

One of the objectives of this thesis was to investigate the extent to which callous unemotional traits (CU) interact with CD. Previous research suggested, in the absence of a standardised tool, that one may combine items from existing standardised measures to create a proxy scale to infer CU traits (Dadds *et al.,*2005). As IMAGEN did not contain a standardised CU scale, items were combined from measures in the IMAGEN battery. Please see Chapter 2 section 2.2 for a reminder of the construct.

***Prevalence of CD and CU***

20% of males and 14% of females reported CD symptoms in the abnormal range as defined by the SDQ, and rated the symptoms as causing a sufficient negative impact to be classed as a CD 'possible' or 'probable' case. There was no main effect of gender within the CD group in terms of symptom count ($F(1,272)$ 0.82, $p>0.05$); males (mean 3.21) and females (mean 3.40) showed equally above average levels of CD symptoms. Neither was there a main effect of gender on the control population ($F(1,1356)$ 0.08, $p>0.05$).

Adolescents were classed as 'High CU' if they scored more than one standard deviation above the mean (a score of 7 or more; scale range 0-13). Overall 18% of the study sample fell into this category; 10% of females (N = 81) and 27% of males (N = 216). See Table 5 for an overlap of both the CD and CU trait for males and females. Males (mean 4.86) rated themselves as significantly more callous compared to females (mean 3.63) ($F(1,1634)$ 118.28, $p<0.001$, eta² 0.061 ). The CD group (mean 5.40) rated themselves as significantly more callous compared to controls (mean 3.97) ($F(1,1633)$ 95.07, $p<0.001$, eta ² 0.055). There was no Gender-by-CD Interaction for CU traits $F(1,1632)$ 0.23, $p>0.05$.

Table 5 Overlap in CD Problems and CU Symptoms for Males and Females

| | Total Study Sample (N=1543) | | | |
|---|---|---|---|---|
| | Males % (N) | | Females % (N) | |
| | CD (N=166) | Control (N=547) | CD (N=115) | Control (N=715) |
| **High CU** | 43% (71) | 27% (145) | 26% (30) | 7% (51) |
| **Average CU** | 57% (95) | 73% (402) | 74% (85) | 93% (664) |

***Data Analysis***

All analyses in this chapter were performed using SPSS V.20. Analyses of covariance (ANCOVA) were conducted using the General Linear Model. Independent factors included CD Group (Case vs. Control), Gender (Male vs. Female) and CU (High vs. Average). Interactions between the factors were explored and two- and three-way interactions were modelled. The main effects were centralised to avoid multicollinearity between the main effect and interaction terms within the model. The full model was modelled first in each instance including all main effects, 2-way interactions and the 3-way interaction. Where the 3-way interaction was not significant the term was removed from the model so that the 2-way interactions could be better investigated. To account for any local differences in recruitment strategy, assessment site was controlled for in all analyses.

***Demographic Information***

Group characteristics (mean, standard deviation) for age and IQ variables may be found in Table 6 and Table 7 and test statistics in Appendix Chapter 3, Table 55. There was a main effect of Group for verbal and performance IQ; in both instances the Control group showed significantly greater scores compared to the CD group (vIQ $F(1,1629)$ 23.19, $p<0.001$, eta² 0.014; pIQ $F(1,1629)$ 15.43, $p<0.001$, eta² 0.009). There was an additional main effect of

gender for verbal IQ; males had a significantly higher verbal IQ than females $F(1,1629)$ 9.74, $p<0.01$, eta² 0.006.

Table 6 Descriptive Statistics: Demographic Variables for Chapter Three [Males Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=71)** | **Average CU (N=69)** | **High CU (N=145)** | **Average CU (N=502)** |
| Age | 14.43 (0.39) | 14.44 (0.41) | 14.37 (0.39) | 14.42 (0.39) |
| Verbal IQ | 110.37 (17.13) | 109.40 (14.59) | 113.72 (16.61) | 113.49 (13.63) |
| Performance IQ | 105.34 (16.09) | 104.63 (16.47) | 109.54 (14.55) | 108.26 (14.14) |

Table 7 Descriptive Statistics: Demographic Variables for Chapter Three [Females Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=30)** | **Average CU (N=85)** | **High CU (N=51)** | **Average CU (N=664)** |
| Age | 14.48 (0.41) | 14.45 (0.43) | 14.42 (0.39) | 14.43 (0.40) |
| Verbal IQ | 106.30 (14.42) | 104.80 (14.82) | 111.84 (16.43) | 110.66 (14.33) |
| Performance IQ | 107.40 (13.82) | 102.35 (14.14) | 109.35 (13.24) | 108.28 (13.67) |

## 3.3 **Results: Clinical Symptoms and Temperament Age 14**

This section reports the main effects and interactions between Group (CD vs. Control), CU (Average vs. High) and Gender (Male vs. Female) and explored the extent to which clinical and temperamental variables at age 14 varied across the cohort. Tables of test statistics may be found in Appendix Chapter 3, Table 56 and Table 57. A table of significant effects follows the descriptive statistics; the most relevant effects (interactions) are discussed in more detail. For each measure a higher score is a measure of a more impaired profile.

Table 8 Descriptive Statistics: Clinical (SDQ) and Temperamental (SURPS) Measures [Males Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=71)** | **Average CU (N=69)** | **High CU (N=145)** | **Average CU (N=502)** |
| Hyperactivity/Inattention | 5.15 (2.67) | 4.98 (2.44) | 3.46 (2.22) | 2.78 (2.04) |
| Emotional Symptoms | 2.65 (2.22) | 2.34 (1.96) | 1.78 (1.80) | 1.80 (1.60) |
| Peer Relationship | 2.24 (1.94) | 2.16 (1.89) | 1.77 (1.73) | 1.31 (1.48) |
| Impulsivity | 13.85 (2.25) | 12.79 (2.15) | 12.48 (2.09) | 11.67 (1.99) |
| Hopelessness | 14.87 (3.35) | 12.91 (3.25) | 13.66 (2.90) | 12.52 (2.43) |

Table 9 Descriptive Statistics: Clinical (SDQ) and Temperamental (SURPS) Measures [Females Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=30)** | **Average CU (N=85)** | **High CU (N=51)** | **Average CU (N=664)** |
| Hyperactivity/Inattention | 4.20 (2.16) | 4.84 (2.32) | 2.24 (2.12) | 2.19 (1.89) |
| Emotional Symptoms | 3.73 (2.15) | 3.87 (2.19) | 4.14 (2.51) | 3.12 (1.99) |
| Peer Relationship | 2.27 (1.82) | 1.60 (1.69) | 1.39 (1.36) | 1.15 (1.39) |
| Impulsivity | 14.40 (2.45) | 12.75 (2.06) | 13.02 (1.89) | 11.92 (2.08) |
| Hopelessness | 14.57 (3.15) | 14.18 (2.47) | 15.04 (2.86) | 12.87 (2.78) |

Table 10 Summary of Significant Main and Interaction Effects: Clinical (SDQ) and Temperamental (SURPS) Measures

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| Hyperactivity/Inattention | × | ✓ | × | ✓ |
| Emotional Symptoms | ✓ | × | × | × |
| Peer Relationship | × | × | × | × |
| Impulsivity | × | × | × | × |
| Negative Thinking | ✓ | × | × | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| Hyperactivity/Inattention | ✓ (CD > Control) | × | ✓ (M > F) | |
| Emotional Symptoms | ✓ (CD > Control) | × | ✓ (F > M) | |
| Peer Relationship | ✓ (CD > Control) | ✓(High>Ave) | ✓ (M > F) | |
| Impulsivity | ✓ (CD > Control) | ✓(High>Ave) | × | |
| Hopelessness | ✓ (CD > Control) | ✓(High>Ave) | ✓ (F > M) | |

*Hyperactivity/Inattention Symptoms*

There was a significant Group-by-CU interaction across the full sample, see Figure 7 on page 84. Post-hoc comparisons showed that within the Control group, High CU was significantly associated with more symptoms of hyperactivity (mean 3.14) compared to the Average CU group (mean 2.45) $F(1,1353)$ 19.81, $p<0.001$, although the size of the effect was small, eta²0.014. Within the CD group there was no such variation as a function of CU group $F(1,272)$ 0.25, $p>0.05$.

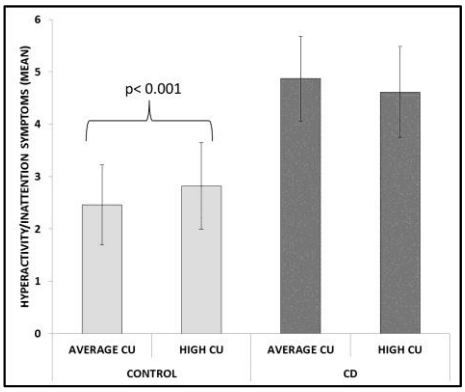


Figure 7 Significant Group-by-CU Interaction for Clinical Symptoms of Hyperactivity/Inattention (error bars 95% CI)

There was also a significant CU-by-Gender Interaction, see Figure 8. Post-hoc comparisons showed males with High CU had significantly greater hyperactivity symptoms (mean 3.97) compared to males with Average CU (mean 3.16) $F(1,804)$ 19.52, $p<0.001$, eta²0.024. Hyperactivity symptoms in females did not vary significantly according to CU group $F(1,821)$ 3.77, $p>0.05$.

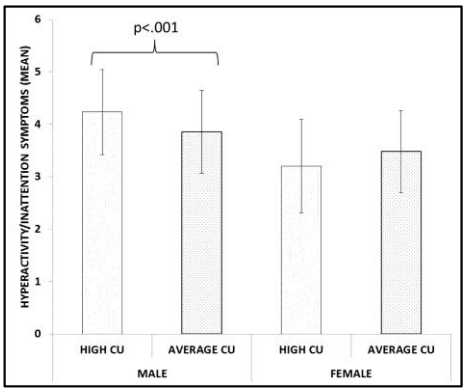


Figure 8 Significant CU-by-Gender Interaction for Clinical Symptoms of Hyperactivity/Inattention (error bars 95% CI)

*Emotional Symptoms*

Here, the findings suggest that when examining males and females with and without CD, CU traits identify a separate group of participants for whom symptoms are worse as indicated by

the significant Group-by-CU-by-Gender interaction ($F$(1,1628) 6.55, $p$<0.05). In males, emotional symptoms did not vary according to CU group in the controls $F$(1,638) 0.02, $p$>0.05, or in the CD group $F$(1,157) 0.65, $p$>0.05. In CD females emotional symptoms did not vary according to CU group; $F$(1,106) 1.02, $p$>0.05, however in female controls there was a significant effect of CU group $F$(1,706) $p$<0.01. The High CU group had significantly more emotional symptoms (mean 3.64) than the Average CU group (mean 2.64) although the effect size was small (partial eta²0.016). See Figure 9.

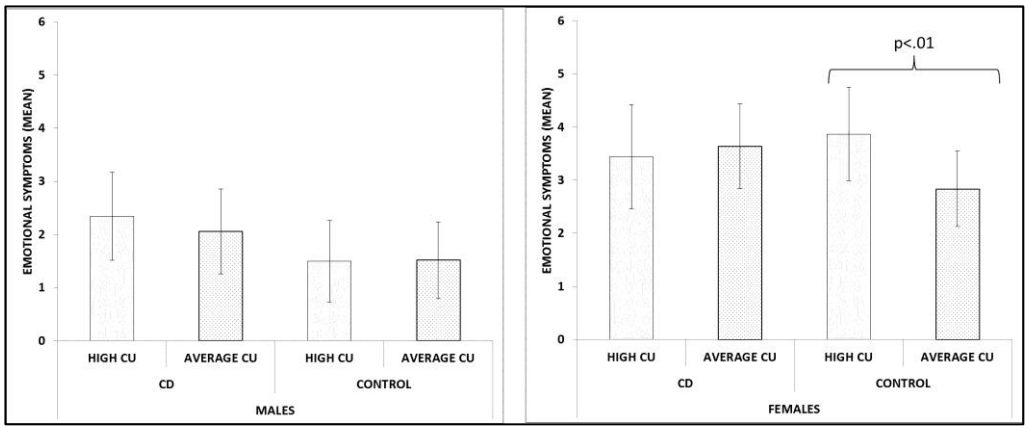


Figure 9 Significant Group-by-CU-by-Gender Interaction for Clinical Symptoms of Emotional Problems (error bars 95% CI)

*Hopelessness*

When examining males and females with and without CD, CU traits also identified a separate group of participants for whom trait hopelessness is exacerbated as indicated by the significant Group-by-CU-by-Gender interaction ($F$(1,1628) 8.85, $p$<0.01) see Figure 10. In males with and without CD problems, High CU was associated with significantly greater trait hopelessness compared to the Average CU groups (Controls $F$(1,638) 21.23, $p$<0.001, eta²0.032; CD $F$(1,157) 8.39, $p$<0.01, eta²0.051). In females the effect was confined to the Control group; the High CU group had significantly greater hopelessness scores (mean 15.51) compared to the Average CU group (mean 13.26) 31.27, $p$<0.001, eta²0.042, there was no such effect in the CD females $F$(1,106) 0.21, $p$>0.05.

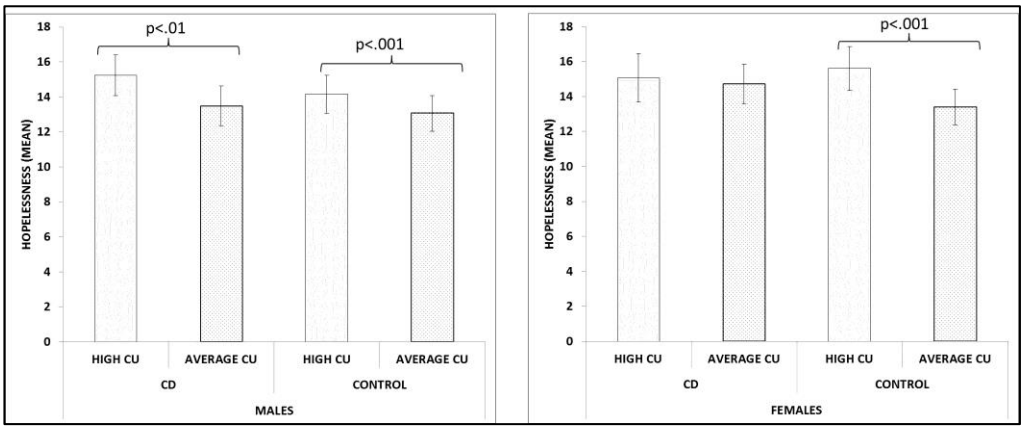


Figure 10 Significant Group-by-CU-by-Gender Interaction for Trait Hopelessness (error bars 95% CI)

## 3.4 **Results: Empathic Concern, Perspective Taking and Personal Distress at Age 16**

This section reports the main effects and interactions between Group (CD vs. Control), CU (Average vs. High) and Gender (Male vs. Female) and explores the extent to which empathy, perspective taking and personal distress measured by the Interpersonal Reactivity Index at age 16 vary across the cohort. A table of significant effects follows the descriptive statistics and the most interesting effects (interactions) are discussed in more detail. Test statistics may be found in Appendix Chapter 3, Table 58 and Table 59. A higher score in each case is associated with greater impairment (e.g. personal distress) or greater ability (e.g. perspective taking, empathic concern).

Table 11 Descriptive Statistics: Interpersonal Reactivity Index Subscales [Males Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Subscale** | **High CU (N=13)** | **Average CU (N=21)** | **High CU (N=46)** | **Average CU (N=237)** |
| Empathic Concern | 15.77 (3.19) | 16.86 (3.77) | 15.13 (3.41) | 17.29 (3.27) |
| Perspective Taking | 15.38 (3.37) | 16.29 (3.25) | 15.04 (3.93) | 16.31 (3.34) |
| Personal Distress | 12.15 (3.05) | 10.71 (3.07) | 12.30 (3.29) | 11.55 (3.23) |

Table 12 Descriptive Statistics: Interpersonal Reactivity Index Subscales [Females Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Subscale** | **High CU (N=8)** | **Average CU (N=34)** | **High CU (N=22)** | **Average CU (N=331)** |
| Empathic Concern | 16.63 (3.66) | 19.94 (3.22) | 16.73 (2.71) | 19.76 (2.96) |
| Perspective Taking | 13.87 (3.18) | 17.64 (4.43) | 15.86 (4.67) | 16.91 (3.45) |
| Personal Distress | 16.63 (2.92) | 14.41 (4.21) | 13.09 (3.46) | 13.66 (3.18) |

Table 13 Summary of Significant Main and Interaction Effects: Interpersonal Reactivity Index Subscales

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| Empathic Concern | × | × | × | × |
| Perspective Taking | × | × | × | × |
| Personal Distress | × | × | ✓ | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| Empathic Concern | × | ✓(Ave > High) | ✓ (F > M) | |
| Perspective Taking | × | ✓(Ave > High) | × | |
| Personal Distress | × | × | ✓ (F > M) | |

*Personal Distress*

There was a significant Group-by-Gender interaction ($F$(1,699) 6.10, $p$<0.05), see Figure 11. In males, personal distress did not vary according to group $F$(1,309) 0.65, $p$>0.05. However, females with CD reported significantly greater personal distress symptoms (mean 14.85) compared to control females (mean 13.67) $F$(1,387) 4.70, $p$<0.05, although this was a small effect (eta²0.012).

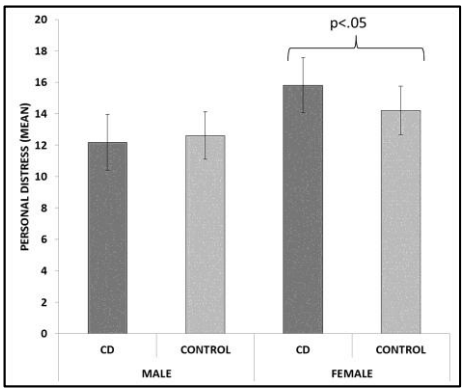


Figure 11 Significant Group-by-Gender Interaction for Personal Distress (error bars 95% CI)

## 3.5 **Discussion**

*This study explored the clinical and temperamental profile of males and females with CD problems, and explored the extent to which callous unemotional traits and gender further moderated these traits. Males and females with CD showed a similar externalising profile to each other showing greater symptoms of hyperactivity and impulsivity compared to controls, and males showed greater symptoms of hyperactivity compared to females, though not on the impulsivity dimension. While in the full sample overall hyperactivity symptoms were unaffected by callous unemotional traits there was a significant interaction whereby in Controls, but not the CD group, High CU was associated with greater symptoms of hyperactivity. High CU in males was also associated with greater symptoms of hyperactivity while females showed no such effects. High CU was associated with greater impulsivity, but there were no significant interaction effects on this trait. Males and females with CD were significantly affected by*

*internalising symptoms, both at the clinical symptom and trait level, and overall females were more affected compared to males on both measures. Callous unemotional traits were associated with greater trait hopelessness and overall moderated internalising symptoms in the CD and control participants.*

***Clinical, Personality and Behavioural Profile; Externalising Symptoms***

This study found that CD was associated with increased symptoms of hyperactivity/inattention in both males and females, consistent with other reports (van Lier *et al.,*2003; Waschbusch, 2003; Frick *et al.,*2003), irrespective of the level of CU traits, CU did not moderate the relationship between CD and Hyperactivity/inattention. This study also found an overall main effect of gender; males showed significantly greater symptoms of hyperactivity/inattention compared to females, however gender did not moderate this effect in the CD or Control groups.

The inclusion of the CU trait meant this study could also investigate whether there were sub-groups of individuals with CD for whom externalising symptoms were worse. Previous work by Frick *et al.,*(2003) found that children with CD and High CU showed significantly greater levels of impairment, although in this study no such effect was identified. Two general effects were found across the cohort; in controls (males and females) High CU was associated with greater symptoms of hyperactivity/inattention, and in males (CD and Control) High CU was associated with greater hyperactive/inattentive symptoms. This suggests that High CU could be associated with a vulnerability, or perhaps serve as a risk factor, for greater symptoms of hyperactivity/inattention in the general population, and may be more pronounced in males, however the size of this effect was very small and so this interpretation would need to be

replicated in an independent sample, and also investigated longitudinally to confirm it's potential value.

This study found that CD was associated with higher trait impulsivity compared to controls, consistent with the report of Castellanos-Ryan, Rubia & Conrod (2011). While there was an overall effect of CU trait in the full sample (High CU was associated with higher trait impulsivity) this did not allow for the identification of a sub-group of CD adolescents that showed significantly greater impairment. It was predicted that CD would be associated with greater peer relationship problems compared to controls and this was the case in terms of measurement using the SDQ. There was also a significant effect of CU; High CU was associated with greater peer relationship problems. There was also a significant main effect of gender, being male was associated with a greater number of peer relationship problems, compared to females.

By and large the effects reported in this study are consistent with those previously reported by Frick et al (2003); both CD and CU traits are associated with behavioural dysregulation evidenced by disinhibited temperamental characteristics such as greater trait impulsivity, more symptoms of hyperactivity/inattention and greater peer difficulties. Collectively, these findings have potentially worrying implications for the both the CD and Control adolescents. As both CD and CU are related to disinhibited behaviours this might put them at increased risk for engaging in negative behaviour such as bullying, acting without thinking and risk taking. These could have a number of consequences for the adolescent; they might become socially isolated, or their academic performance might be hindered due to an inability to concentrate and plan ahead. As the adolescent progresses through puberty these traits may become more stable, which could have negative consequences for the adolescent later in adulthood, however the

predictive validity and also temporal stability of these traits would need to be explored longitudinally to explore this proposition.

***Clinical, Personality and Behavioural Profile; Internalising Symptoms***

Consistent with the findings of Maughan *et al.,*(2004) and Polier *et al.,*(2012) this study found that CD was associated with greater symptoms of emotional problems using a clinical (SDQ) and temperamental (SURPS; Hopelessness) measure. There was also a significant main effect of gender for both measures; females reported significantly more emotional symptoms and reported feeling more hopeless compared to males. This reflected the commonly reported finding that females show greater negative emotionality compared to males (e.g. see Cukrowicz, Taylor, Schatschneider, & Iacono, 2009).

The inclusion of the CU trait revealed some interesting sex-specific interaction effects. Consistent with the report of Pardini *et al.,*(2012) in CD females symptoms across both dimensions did not vary according to CU trait, they were elevated anyway. However, in contradiction to the findings of Pardini *et al.* this study found significantly elevated levels of internalising symptoms in Control females with High CU across both dimensions compared to those with Average CU, and were as affected by internalising symptoms (depression/anxiety) as CD females with High CU. In males there was no such interaction effect in the clinical dimension, however for temperament males with and without CD problems had higher trait hopelessness if they also had High CU. It appears that in females without CD High CU might be considered a risk factor for the development of internalising symptoms, although this would need to be investigated in a longitudinal study, while in males High CU can exacerbate a temperamental measure of negative emotionality. This study also found evidence suggesting that overall females were more emotionally reactive than males. Using the Interpersonal

Reactivity Index (IRI; Personal Distress) measured at age 16 the study found that females with CD reported significantly greater symptoms of distress and discomfort in response to distress in others compared to females without CD. No such effect was observed in males and this finding did not vary as a according to CU traits.

With regards to internalising symptoms it is difficult to unpick whether the effects here might be associated with their externalising behavioural difficulties. For instance, the experience of peer relationship problems could cause distress related to relative social isolation or exclusion, which in turn may result in negative emotional symptoms such as hopelessness. One method to test this hypothesis would be to examine the extent to which the CD and CU constructs are related to the frequency of victimisation in the CD and High CU groups. It is possible that these females are not only aggressors, but might also be victims of negative behaviours.

***Empathy and Perspective Taking Ability***

Females rated themselves as more empathic than males, a finding consistent with other research (Lawson, Baron-Cohen & Wheelwright, 2004; Munoz, Qualter & Padgett, 2011). There had been an expectation that the study would find a main effect for group in which CD problems would be associated with reduced empathic concern, however no such effect was observed. This study did however find an overall main effect of CU; Average CU was associated with significantly greater empathic concern compared to the High CU group consistent with (Munoz *et al.,*2011), although contrary to expectation CU did not moderate the effect of the other factors.

Somewhat unexpectedly there was also a main effect of CU on the perspective-taking trait; previous work had indicated that there would be no significant difference in perspective-taking

ability as a function of CU (Jones *et al.,*2010). This might be due, at least in part, to the way empathy and perspective taking ability were assessed. Previous studies reporting empathy impairments and intact perspective taking ability in individuals with CD problems used experimental paradigms where situations were depicted using video clips (de Wied, van Boxtel, Matthys, & Meeus, 2012), or vignettes (Jones *et al.,*2010). It could be that empathy and perspective-taking ability, or indeed impairment, is best assessed using paradigms that mimic real-life situations rather than relying solely on self-reported traits.

***Limitations***

One limitation of this study was the use of a proxy CU scale, rather than one of the widely available validated measures; however the effects reported here are in line with evidence from previous studies, suggesting that the CU scale was sufficient in the absence of one of the preferred measures. An additional limitation of the proxy CU scale is that it is self-rated. Ideally one would use ratings from the respondent's parents and teachers when examining CU; however it was not possible to generate such a proxy measure using the Imagen sample measures. This means the measure itself is less objective than one would like. This study may be have been limited by the threshold used for the identification of individuals with 'High CU'. As mentioned in Chapter 2 section 2.2 this threshold was selected to maximise the number of participants in each group, although this might have hindered the identification of between-group differences. Nevertheless this method has been adopted by other published research groups; some favoured a median split for their identification of 'High' CU traits (e.g. Jones *et al.,*2010). In an ideal study one would compare the extreme ends of the distribution; examining those with high vs. low CU traits. With the exception of some of the main effects the interaction and post-hoc comparison effects reported in this study have relatively modest to small effect sizes, so the extent to which one may draw inferences about these data are reduced. This may be exacerbated by the use of a dichotomous classification where those

individuals with more severe forms of CD were relatively few, and were not closely matched to a control group.

***Conclusion***

In terms of internalising and externalising symptoms this study suggested that males and females with CD problems were similar to one another. The CU trait, by and large, did not allow for the distinction between CD groups in any of the externalising variables. This study provides evidence that High CU is associated with internalising symptoms in females, although a careful longitudinal replication would be required to establish the predictive validity of the CU trait. In general it appears that both CD and CU are characteristic of an adolescent low in behavioural inhibition who also has little resonance with others, e,g, low empathic concern, and who does not adequately regulate their behaviour (impulsivity/hyperactivity inattention problems) and makes antisocial, undesirable behaviour (peer relationship difficulties). As CU is associated with additional difficulties e.g. substance use problems (Wymbs *et al.,*2012) these findings do reinforce the clinical utility of assessing CU traits as a matter of course.

# Chapter 4 Neural Basis of Emotion Dysregulation in Conduct Disorder

*Neural reactivity to emotional stimuli has previously been investigated in individuals with conduct disorder; however few studies have investigated sex differences in brain function during emotion processing. This chapter describes a neuroimaging study investigating patterns of neural reactivity in response to the passive viewing of emotional stimuli in participants with conduct disorder problems, and explored whether this reactivity was further moderated by gender and callous-unemotional traits*

## 4.1 Introduction

Interpreting emotions that "manifest in uniquely recognisable and stereotyped behavioural patterns of facial expression" (Dolan, 2002) is an important ability for human social interaction. Emotional expressions may be adaptive; a person might modify their behaviour based on the interpretation of emotional signals, a welcoming smile signals it is safe to approach, while a fearful or angry expression might indicate it is time to flee. Emotional expressions can convey intent and can give the 'reader' an insight into the state of mind of another person. As such, humans base their actions largely on the interpretation of emotional expressions. In a review of the literature, Vuilleumier (2005) asserted that humans tend to pay more attention to emotional rather than neutral stimuli, and presented evidence suggesting that 'emotional biases are stronger with "biologically prepared" stimuli (e.g. faces) and with negative or threat-related emotions (e.g. fear or anger)'. This study focuses specifically on the investigation of processing angry faces.

***Disrupted Emotion Processing in CD and Psychopathy/Callous Unemotional Traits***

Behavioural difficulties associated with emotion dysregulation may be a consequence of a person's inability to accurately express or control their reactions to the presentation of emotion (e.g. reading the emotional expression of another person in a social situation), or a failure to manage or monitor their own vicarious experience of emotion. A number of studies have found evidence for emotional reactivity dysfunction (physiological) in individuals with CD problems, reviewed in Chapter One, section 1.4.

Behavioural paradigms suggest that individuals with CD problems have difficulty recognising negatively valenced emotions compared to control subjects. Emotion recognition paradigms tested in clinical samples have found that male youths with E-O or A-O CD are worse at recognising anger, disgust and happiness, while the E-O group are also worse at recognising fear (Fairchild, Van Goozen, Calder *et al.,*2009). Separate investigations working with females with CD have found evidence suggesting that they are worse at recognising anger and disgust (Fairchild *et al.,*2010), although these findings are mixed. A relatively recent community investigation found no evidence for emotion recognition deficits for females with CD (Pajer *et al.,*2010). Behavioural evidence also exists suggesting that CU traits are associated with disrupted emotion processing. Emotion recognition paradigms tested in clinical samples have found that high CU traits are associated with impairments in processing sadness and fear (Blair *et al.,*2001; Fairchild *et al.,*2010; Stevens *et al.,*2001), see Table 16 and Table 17.

There is evidence to suggest that the emotion recognition deficits in youths with CD with and without CU traits may have a neural basis. fMRI paradigms have investigated emotion processing in youths with CD problems. Working with a clinical group of older adolescents and young adults, Passamonti and colleagues found evidence for reduced neural responses in the

amygdala, ventromedial prefrontal cortex, orbitofrontal cortex and insula during the observation of angry emotional stimuli (Passamonti *et al.,*2010). Community recruited clinical samples of youths with CD have found that CD problems plus high CU traits is associated with reduced amygdala reactivity in response to fearful, but not angry or neutral stimuli (Jones *et al.,*2009; Marsh *et al.,*2008; Viding *et al.,*2012) . See Table 14 - Table 17 for details of some of the studies that have investigated emotion processing in individuals with CD problems using behavioural and fMRI paradigms.

Taken together, both the behavioural and neuroimaging findings suggest that youths with CD appear to have difficulty processing emotions with negative valence; those emotions most likely to trigger a response e.g. fight or flight, and all of the studies presented suggest there may be dysfunction in the amygdala.

Table 14 Summary of Behavioural Findings: Emotional Dysregulation in CD

| **Behavioural Evidence** | | | | | | |
|---|---|---|---|---|---|---|
| **Authors** | **Task** | **Age Group** | **Sample** | **Gender** | **Comparison** | **Impaired Emotion Recognition** |
| Fairchild, Van Goozen, Calder, Stollery & Goodyer (2009) | Emotion Recognition | 14-18 | Clinical A-O CD (N=39) E-O CD(N=42) Control(N=40) | Male | Control > E-O Control > A-O | Anger, Disgust, Happiness Fear |
| Fairchild, Stobbe, Van Goozen, Calder & Goodyer (2010) | Emotion Recognition | 14-18 | Clinical CD (N=25) Control(N=30) | Female | Control > CD | Anger, Disgust |
| Pajer, Leininger & Gardner (2010) | Emotion Recognition | 15-17 | Community CD (N=35) Control(N=30) | Female | Control vs. CD | No effect |
| d'Acremont and Van der Linden (2007) | Emotional Face Memory | 13-17 | Community (N=86) | M & F | | Conduct problems were associated with memory bias for angry faces |

A-O CD= Adolescence Onset Conduct Disorder / E-O CD = Early Onset Conduct Disorder

Table 15 Summary of fMRI Findings: Emotional Dysregulation in CD

| **fMRI Evidence** | | | | | | |
|---|---|---|---|---|---|---|
| **Authors** | **Contrast** | **Age Group** | **Sample** | **Gender** | **Comparison** | **Impaired Function** |
| Passamonti, Fairchild, Goodyer, Hurford,<br><br>Hagan, Rowe & Calder 2010 | Angry vs. Neutral Faces<br><br>Sad vs. Neutral Faces | 16-21 | Clinical<br><br>A-O CD(N=25)<br><br>E-O CD(N=27)<br><br>Control(N=23) | Male | Control > E-O & A-O CD<br><br>Control > E-O | Amygdala, ventro-medial prefrontal cortex,<br><br>orbitofrontal cortex, insula<br><br>Amygdala |
| Herpertz, Huebner, Marx, Vloet, Fink, Stoecker, Shah, Konrad & Herpertz-Dahlmann 2008 | Negative vs. Neutral | 12-17 | Clinical<br><br>E-O CD(N=22)<br><br>Control(N=22) | Male | E-O > Control | Amygdala |

A-O CD= Adolescence Onset Conduct Disorder / E-O CD = Early Onset Conduct Disorder

Table 16 Summary of Behavioural Findings: Emotional Dysregulation in CD ± CU or Psychopathy

| **Behavioural Evidence** | | | | | | |
|---|---|---|---|---|---|---|
| **Authors** | **Task** | **Age Group** | **Sample** | **Gender** | **Comparison** | **Impaired Emotion Recognition** |
| Blair, Colledge, Murray & Mitchell, 2001 | Morphed Emotional Faces<br><br>(sensitivity to subtle changes in emotional expression) | 9-17 | High Psychopathy (N=20)<br><br>Controls (N=31) | Male | Control > Psychopathy | Sad, Fear |
| Fairchild, Stobbe, Van Goozen,<br><br>Calder & Goodyer (2010) | Emotion Recognition | 14-18 | Clinical<br><br>CD (N=25)<br><br>Controls (N=30) | Female | CD-Psychopathic Traits > CD+Psychopathic Traits | Sad |
| Guyer , McClure, Adler, Brotman, Rich, Kimes, Pine, Ernst Leibenluft (2007) | Emotion Recognition | 7-18 | Clinical<br><br>ADHD/CD (N=35)<br><br>Controls (N=92) | M & F | No effect | No Effect |
| Stevens, Charman & Blair (2001) | Emotion Recognition | 9-15 | Clinical<br><br>DBD+Psychopathy(N=9)<br><br>DBD (N=9) | Male | DBD > DBD+Psychopathy | Sad, Fear<br><br>No effect for happy, angry |

DBD = Disruptive Behaviour Disorder (e.g. Attention Deficit Hyperactivity Disorder [ADHD]/Conduct Disorder [CD]/Oppositional Defiant Disorder [ODD])

Table 17 Summary of fMRI Findings: Emotional Dysregulation in CD ± CU or Psychopathy

| **fMRI Evidence** | | | | | | |
|---|---|---|---|---|---|---|
| **Authors** | **Task** | **Age Group** | **Sample** | **Gender** | **Comparison** | **Impaired Emotion Recognition** |
| Carre, Hyde, Neumann, Viding, and Hariri (2012) | Face Matching Task | Mean 19.65 | Community (N=200) | M & F | Characterising psychopathic traits in a healthy population sample | Interpersonal trait (cunning/manipulative) negatively associated with amygdala reactivity to fear. Lifestyle trait (risk-taking, impulsive) positively associated with amygdala reactivity to anger |
| Jones, Laurens, Herba,<br><br>Barker & Viding (2009) | Emotion Recognition | Mean 11 | Community Recruited, CD+CU (N=17), Controls (N=13) | Male | Control > CD+CU | Amygdala; Fear |
| Marsh, Finger, Mitchell, Reid, Sims, Kosson, Towbin, Leibenluft, Pine & Blair (2008) | Emotion Recognition | 10-17 | CD/ODD+CU(N=12)<br><br>ADHD (N=12)<br><br>Control (N=12) | M & F | Control, ADHD > CD/ODD+CU | Amygdala; Fear<br><br>No effect for Anger/Neutral |
| Viding, Sebastian, Dadds, Lockwood, Cecil, De Brito & McCrory (2012) | Emotion Recognition | 10-16 | Community Recruited<br><br>CD+CU (N=15)<br><br>CD-CU (N=15)<br><br>Control (N=16) | Male | CD-CU > Controls, CD+CU | Amygdala; Fear |

***Amygdala: Candidate brain region of interest***

There are a number of brain regions involved in emotion and face processing (see review by Fusar-Poli *et al.,*2009). This study focuses specifically on emotion dysregulation in youths with CD problems, therefore, on the basis of previous findings, the amygdala was selected as the candidate brain region of interest.

The amygdala was initially identified by Adolphs and colleagues as a structure specifically involved in processing negatively valenced emotions. Their investigations revealed that bilateral amygdala damage in a group of patients resulted in a loss of perceived intensity for expressions of fear, anger and surprise compared to controls (Adolphs, Tranel, Damasio, & Damasio, 1994) and this effect appeared exclusive to negative emotions (e.g. fear, anger and disgust); their later study found no such differences were observed in the ratings of happy faces compared to control subjects (Adolphs *et al.,*1999). A review by Davis and Whalen (2001) summarised evidence from primate and human studies and suggested that the amygdala is key for a number of processes; fear conditioning, emotional reactivity, vigilance, processing face expressions, motor behaviour and attentional processes. Taken together this evidence suggests that the amygdala is primarily associated with the emotions that trigger withdrawal, and despite recent evidence showing that the amygdala responds to both negative and positive stimuli (Sergerie, Chochol, & Armony, 2008) it remains 'an important mediator of emotional influences on perception' (Dolan, 2002).

The amygdala has not been the only area implicated as being aberrant in function in youths with CD, indeed the orbitofrontal cortex would have also represented a potentially fruitful region of interest to study. However the amygdala is the region that has been most frequently reported to show aberrant function, and to reduce the number of corrections for multiple

comparison, only the amygdala was selected. To compensate for this more restricted approach a whole brain analysis was also included to explore where patterns of reactivity might vary across the whole brain.

***Gender Differences in Emotion Recognition***

There is evidence suggesting that males and females might process emotional stimuli in different ways. For instance, Donges and colleagues found that females are more prone to 'affective priming'; where the presentation of an emotional facial expression influences subsequent judgements, compared to males, especially for positive (happy) stimuli, males showed no such effects (Donges, Kersting, & Suslow, 2012). There is also evidence to suggest that males and females differ in their perception of stimulus intensity. Biele and Grabowska (2006) investigated sex differences in the perception of emotional intensity using dynamic and static emotional stimuli and found that females judged anger as more intense than happiness, and that dynamic stimuli were more intense than static. Males also rated anger as more intense but only when the stimuli were dynamic. A recent review by Kret and De Gelder (2012) presented evidence suggesting that males show greater amygdala responses compared to females during the observation of negative emotions, (see Schneider *et al.,*2011 for findings from the IMAGEN study), and suggest that emotional stimuli provide different kinds of 'behaviourally relevant cues' to males. Consequently, as sex differences in BOLD response have been reported for the amygdala in addition to wider brain regions this study also investigated the main and interaction effects of sex on amygdala and whole brain responses during the presentation of negative stimuli.

***Predictions***

It has been suggested that the processing of negatively valenced emotions may be impaired in individuals with CD with and without Psychopathy/Callous-Unemotional traits. This study investigated amygdala function using an fMRI paradigm that presented dynamic angry faces, as they represent a good ecologically valid threat. Based on the findings of previous studies it was predicted that there would be a main effect of group; adolescents with CD problems would show a reduced magnitude BOLD response to angry faces compared to control adolescents. As there is a growing body of evidence suggesting that males and females process negative information in different ways the main effect of gender was explored. The extent to which CU traits further moderated these effects was investigated. While there have been no reported associations between CU traits and anger processing, it was expected that high CU would be associated with reduced magnitude BOLD responses. Exploratory whole brain analyses were also performed investigating the extent to which gender and CU moderated reactivity in CD and Control adolescents.

## 4.2 **Method**

***Participants***

Participants with Conduct Disorder Problems (CD) were those classed as 'possible' or 'probable' CD cases (N=273) according to the Strengths and Difficulties Questionnaire (SDQ). All participants classed as 'unlikely' to develop CD are referred to as Controls (N=1370). For full details please see Chapter Two, section 2.2. Adolescents with 'High CU' were those who scored more than one standard deviation above the mean (a score of 7 or more; N=295), the 'Average CU' group were those who scored between 0-6 points (N=1358), see Chapter Two, section 2.2 for further information.

***Demographic Information***

Test statistics for demographic variables may be found in Appendix Chapter 4, Table 60. There was a significant main effect of Group for verbal and performance IQ; the control group had significantly greater IQ scores compared to the CD group (vIQ $F(1,1573)12.32$, $p<0.001$; pIQ $F(1,1573)12.40$, $p<0.001$. There was a main effect of Group for Hyperactivity/Inattention symptoms; the CD group had significantly more symptoms than the Controls $F(1,1629)$ 187.34, $p<0.001$. There was a main effect of gender on two measures; verbal IQ and Hyperactivity/Inattention symptoms; males had a significantly greater score compared to females (vIQ $F(1,1573)$ 7.42, $p<0.01$; H/I $F(1,1629)$ 14.89, $p<0.01$). There was also a significant Gender-by-CU interaction for symptoms of Hyperactivity/Inattention ($F(1,1629)4.24$, $p<0.05$); males with High CU had significantly greater symptoms compared to females with High CU ($p<0.001$) and males with Average CU also had significantly greater symptoms compared to females with Average CU ($p<0.05$).

Table 18 Descriptive Statistics: Demographic Variables for Chapter Four [Males; Mean (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| **Measure** | **High CU (N=68)** | **Average CU (N=80)** | **High CU (N=140)** | **Average CU (N=493)** |
| Age | 14.42 (0.42) | 14.44 (0.36) | 14.37 (0.37) | 14.41 (0.40) |
| Verbal IQ | 111.49 (16.96) | 110.34 (16.63) | 113.74 (17.31) | 112.79 (14.41) |
| Performance IQ | 104.38 (17.05) | 105.78 (16.37) | 108.9 (15.13) | 108.05 (13.94) |
| Hyperactivity/Inattention | 5.09 (2.82) | 4.74 (2.35) | 3.36 (2.18) | 2.77 (2.06) |
| Emotional Symptoms | 2.76 (2.38) | 2.29 (1.96) | 1.91 (1.90) | 1.77 (1.58) |

Table 19 Descriptive Statistics: Demographic Variables for Chapter Four [Females; Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=32)** | **Average CU (N=93)** | **High CU (N=55)** | **Average CU (N=682)** |
| **Age** | 14.42 (0.39) | 14.43 (0.46) | 14.39 (0.40) | 14.43 (0.40) |
| **Verbal IQ** | 107.35 (17.18) | 105.27 (16.46) | 111.51 (15.86) | 110.13 (14.75) |
| **Performance IQ** | 109.16 (14.69) | 102.8 (14.20) | 109.75 (14.25) | 107.92 (14.39) |
| **Hyperactivity/Inattention** | 4.41 (2.33) | 4.67 (2.37) | 2.09 (2.07) | 2.16 (1.87) |
| **Emotional Symptoms** | 3.75 (2.38) | 3.78 (2.34) | 4.31 (2.61) | 3.08 (2.01) |

Participants with complete data that passed task specific outlier criteria in terms of movement, spike detection, were able to view the task stimuli without obstruction and did not show anatomical abnormalities were included in the analysis for the angry vs. control contrast (N=1643). Of this dataset, N=1527 participants were available for region of interest analysis for the ambiguous vs. control contrast.

***fMRI Data Acquisition and Analysis***

Structural and functional MRI data were acquired at eight IMAGEN assessment centres with 3T MRI scanners of different manufacturers, as described in Chapter Two, section 2.3. The task was administered as part of a larger battery of tasks during the first of two imaging acquisition sessions; please see Chapter Two, section 2.3.

***Random Effects Analysis***

In the second level random effects analysis one sample t-tests were used to identify brain regions that showed significantly greater activation in: (i) angry vs. control blocks and (ii)

ambiguous vs. control blocks. Summary statistical maps were thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for gender, site and handedness.

***Region of Interest (ROI) Analysis***

An amygdala ROI was extracted based on the peak from the random effects analysis of the full sample of the angry vs. control contrast (xyz ±21 -7 -14, 8mm sphere). The beta values for the BOLD response to angry faces vs. control stimuli and ambiguous faces vs. control stimuli were averaged across all voxels within the ROIs using the MARSBAR toolbox (http://marsbar.sourceforge.net) and the data exported for group-level analyses in SPSS. All ROI analyses were conducted using SPSS V.20. Analyses of covariance (ANCOVA) were conducted using the General Linear Model. Independent factors included Group (CD vs. Control), gender and CU (High vs. Average). Interactions between the factors were explored and two- and three-way interactions were modelled. The full model was examined first in each instance to include all main and interaction effects. Where the 3-way interaction was not significant the term was removed from the model so that the 2-way interactions could be better investigated. To account for local differences in recruitment strategy, and between-site differences in fMRI scanner, site was controlled for in all analyses. For all imaging analysis handedness (left/right/ambidextrous) was controlled for.

***Whole Brain Analysis***

Main effects for gender, Group (CD vs. Control), CU (High vs. Average) and interactions for Gender-by-Group, Gender-by-CU, Group-by-CU and Gender-by-Group-by-CU were examined using regression analyses controlling for site, handedness and hyperactivity/inattention symptoms.

## 4.3 Results: Random Effects and Region of Interest Analysis

The results are reported in three sections, beginning with the random effects analysis, moving on to the region of interest analysis of the amygdala and finishing with the exploratory whole brain analysis.

***Random Effects Analysis***

In the second level random effects analysis one sample t-tests were used to identify brain regions that showed significantly greater activation in: (i) angry vs. control blocks and (ii) ambiguous vs. control blocks. Summary statistical maps were thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for gender, site and handedness. For activation in the angry vs. control blocks please see Figure 12 and Table 20. For activation in the ambiguous vs. control blocks please see Appendix Chapter 4, Figure 27 and Table 61.

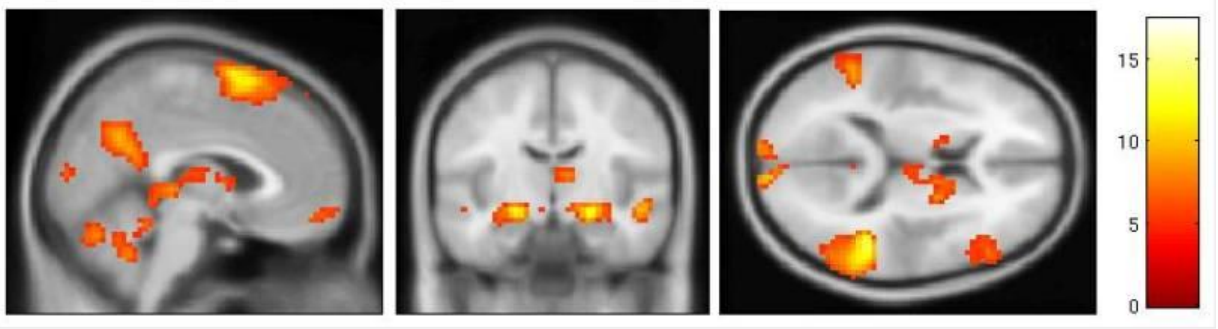


Figure 12 Random Effects Clusters for the Emotional Reactivity Task 'Angry vs. Control Contrast' (Full Sample)

Table 20 Significant Random Effects Clusters for the Emotional Reactivity Task 'Angry vs. Control Contrast' (Full Sample)

| | | | | | Cluster |
|---|---|---|---|---|---|
| **Region (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Temporal Occipital Fusiform Cortex, Inferior Temporal Gyrus, Bilateral Amygdala | | 42 -46 -23 | 3897 | Inf | <.001 |
| Inferior Frontal Gyrus (triangularis & opercularis), Precentral gyrus, Middle Frontal Gyrus | 6/45 | 48 20 25 | 1131 | Inf | <.001 |
| Superior Frontal Gyrus | 6 | 6 17 67 | 380 | Inf | <.001 |
| Middle Temporal Gyrus, Supramarginal Gyrus, Superior Temporal Gyrus | | -54 -46 7 | 235 | Inf | <.001 |
| Inferior Frontal Gyrus (pars opercularis), Middle Frontal Gyrus, Precentral Gyrus | 6/4 | -42 17 25 | 301 | Inf | <.001 |
| Cerebellum | | -12 -76 -29 | 234 | Inf | <.001 |
| Precuneus | | 3 -61 31 | 150 | Inf | <.001 |
| Cerebellum | | 0 -55 -38 | 111 | Inf | $2.22^{-16}$ |
| Lingual Gyrus | | 12 -70 7 | 47 | 6.92 | $5.07^{-10}$ |
| Frontal Operculum cortex, Orbitofrontal Cortex, Insula | | -42 26 1 | 45 | 6.77 | $8.64^{-10}$ |
| Caudate, Thalamus | | -9 5 4 | 49 | 6.8 | $2.30^{-10}$ |
| Medial Prefrontal Cortex | 10 | 6 53 -14 | 34 | 6.6 | $1.90^{-08}$ |
| Temporal Pole, Middle Temporal Gyrus, Superior Temporal Gyrus | 21 | -51 2 -23 | 25 | 6.01 | $3.08^{-07}$ |
| Superior Frontal Gyrus, Frontal Pole | 9 | 6 56 31 | 12 | 5.8 | $3.52^{-05}$ |

***Results: Region of Interest Analysis***

Consistent with previous reports (Manuck, Brown, Forbes, & Hariri, 2007) the angry vs. control contrast elicited robust bilateral activation of the amygdala. As there were no a priori hypotheses regarding which hemisphere was most relevant, a correction for bilateral comparison was applied to the statistical threshold [$p_{corr}$<0.025]. There were no significant effects for the Ambiguous vs. Control contrast see Appendix Chapter 4, Table 63, significant effects were found only for the Angry vs. Control contrast. A summary of significant main and interaction effects may be found on Table 21.

Table 21 Summary of Significant Main and Interaction Effects Region of Interest Analyses Emotional Reactivity fMRI Paradigm

| | Interactions | Group-by-CU-by-Gender | Group-by-CU | Group-by-Gender | Gender-by-CU |
|---|---|---|---|---|---|
| Angry vs. Control | L Amygdala | × | × | × | × |
| | R Amygdala | × | × | ✓ | × |
| Ambiguous vs. Control | L Amygdala | × | × | × | × |
| | R Amygdala | × | × | × | × |
| | Main Effects | Group | CU | Gender | |
| Angry vs. Control | L Amygdala | × | × | × | |
| | R Amygdala | × | × | × | |
| Ambiguous vs. Control | L Amygdala | × | × | × | |
| | R Amygdala | × | × | × | |

Table 22 Descriptive Statistics for the Emotional Reactivity Task Contrasts Amygdala Region of Interest: Males Mean Beta Values (SD)

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Angry Faces vs. Control** | **High CU (N=68)** | **Average CU (N=80)** | **High CU (N=140)** | **Average CU (N=493)** |
| L Amygdala | 0.32 (0.32) | 0.35 (0.39) | 0.35 (0.37) | 0.35 (0.38) |
| R Amygdala | 0.32 (0.41) | 0.37 (0.37) | 0.43 (0.37) | 0.44 (0.37) |
| **Ambiguous Faces vs. Control** | **High CU (N=63)** | **Average CU (N=73)** | **High CU (N=124)** | **Average CU (N=452)** |
| L Amygdala | 0.26 (0.32) | 0.26 (0.32) | 0.29 (0.30) | 0.28 (0.32) |
| R Amygdala | 0.39 (0.35) | 0.35 (0.28) | 0.40 (0.29) | 0.36 (0.33) |

Table 23 Descriptive Statistics for the Emotional Reactivity Task Contrasts Amygdala Region of Interest: Females Mean Beta Values (SD)

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Angry Faces vs. Control** | **High CU (N=32)** | **Average CU (N=93)** | **High CU (N=55)** | **Average CU (N=682)** |
| L Amygdala | 0.26 (0.27) | 0.34 (0.34) | 0.27 (0.30) | 0.30 (0.34) |
| R Amygdala | 0.37 (0.24) | 0.39 (0.34) | 0.28 (0.28) | 0.36 (0.34) |
| **Ambiguous Faces vs. Control** | **High CU (N=29)** | **Average CU (N=85)** | **High CU (N=53)** | **Average CU (N=646)** |
| L Amygdala | 0.34 (0.22) | 0.26 (0.27) | 0.30 (0.29) | 0.30 (0.30) |
| R Amygdala | 0.42 (0.22) | 0.38 (0.30) | 0.40 (0.31) | 0.40 (0.32) |

***Gender-by-Group Interaction***

There was a significant Gender-by-Group interaction in the right amygdala (see Figure 13). CD Males showed reduced right amygdala activity compared to Control males ($p$<0.05), however in the females there was no difference in amygdala activity as a function of group (CD vs. Control). This interaction effect remained significant when symptoms of Hyperactivity/Inattention, Verbal IQ and Emotional symptoms (F(1,1569) 5.76, $p$<0.05, eta²

0.004) were also controlled for, although the effect size became very small. There was no significant interaction effect in the left amygdala.

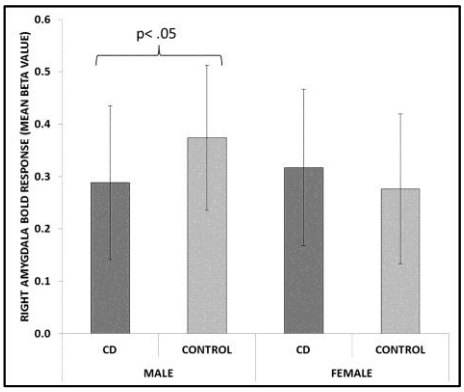


Figure 13 Region of Interest Analysis: Significant Gender-by-Group Interaction for the Emotional Reactivity Task 'Angry vs. Control' Contrast in the Right Amygdala (error bars 95% CI)

## 4.4 **Results: Whole Brain Analysis**

Statistically significant differences are reported as voxel-intensity T-values for clusters at $p<0.05$ family wise error corrected (FWE) and clusters were thresholded to a minimum of 10 voxels. There were significant main effects for gender and CU, and two significant interaction effects; Gender-by-CU and Group-by-CU, see Table 25. There was no significant main effect of Group, no significant Gender-by-Group interaction and no Group-by-Gender-by-CU interaction, see Table 24.

Table 24 Summary of Significant Main and Interaction Effects Whole Brain Analyses Emotional Reactivity fMRI Paradigm

| Interactions | Group-by-CU-by-Gender | Group-by-CU | Group-by-Gender | Gender-by-CU |
|---|---|---|---|---|
| Angry vs. Control | × | ✓ | × | ✓ |
| Main Effects | Group | CU | Gender | |
| Angry vs. Control | × | ✓ | ✓ | |

***Main effect of Gender***

Males showed significantly greater BOLD responses in a cluster including the right precuneus and posterior cingulate gyrus, and a cluster including the right medial prefrontal cortex and paracingulate cortex, see Table 25 and Figure 14. Females showed significantly greater responses compared to males bilaterally in the fusiform cortex, bilaterally in the supramarginal cortex, in the occipital cortex and the superior parietal lobule. See Table 25 and Figure 15

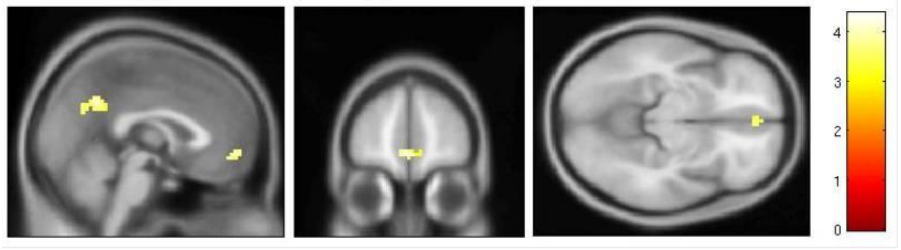


Figure 14 Whole Brain Analysis Emotional Reactivity Task: Males > Females

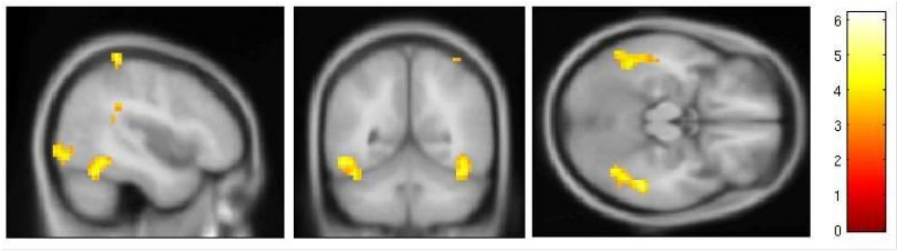


Figure 15 Whole Brain Analysis Emotional Reactivity Task: Females > Males

Table 25 Exploratory Whole Brain Analysis: Significant Main and Interaction Effects

| **Main Effect** | **Region** | **BA** | **X Y Z** | **K** | **T** | ***p*-value** |
|---|---|---|---|---|---|---|
| **Gender** | | | | | | |
| Males > Females | (R) Precuneus, Posterior Cingulate Gyrus | 7/31 | 3 -55 34 & 0 -67 28 | 65 | 4.38 | .002 |
| | (R) Medial Prefrontal Cortex and Paracingulate Gyrus | | 9 59 -5 & 0 53 -8 | 46 | 4.24 | .015 |
| Females > Males | (R) Lateral Occipital Cortex | 19 | 51 -79 -2 & 57 -67 -2 | 108 | 6.22 | $5.37^{-5}$ |
| | (R) Supramarginal Gyrus | 40 | 51 -40 31 & 63 -43 28 & 63 -40 43 | 96 | 5.55 | $1.44^{-4}$ |
| | (R) Fusiform Gyrus | | 42 -58 -23 & 51 -40 -17 & 42 -55 -14 | 126 | 5.05 | $1.31^{-5}$ |
| | (L) Fusiform Gyrus, Inferior Temporal Gyrus | | -45 -49 -14 & -42 -55 -23 & -51 -40 -17 | 129 | 5.05 | $1.04^{-5}$ |
| | (L) Supramarginal Gyrus, Inferior Temporal Gyrus | | -60 -46 52 & -63 -34 52 & -48 -49 64 | 100 | 4.71 | $1.03^{-4}$ |
| | (R) Superior Parietal Lobule | | 42 -40 70 & 36 -52 67 & 30 -46 76 | 84 | 4.68 | $4.03^{-4}$ |
| **CU** | **Region** | **BA** | **X Y Z** | **K** | **T** | ***p*-value** |
| High CU > Average CU | (R) Caudate, Nucleus Accumbens, Putamen | | 12 20 7 & 6 11 1 & 21 23 -2 | 41 | 3.66 | .026 |
| **Gender-by-CU Interaction** | **Region** | **BA** | **X Y Z** | **K** | **T** | ***p*-value** |
| Females High CU > Ave CU (No effect in Males) | (L) Caudate, white matter (Fornix) and ventricle | | -3 8 7 & -3 -1 16 | 36 | 4.06 | .046 |
| **Group-by-CU Interaction** | **Region** | **BA** | **X Y Z** | **K** | **T** | ***p*-value** |
| CD+CU greater hypoactivation > CD-CU (No effect in Controls) | (R) Cuneus and Precuneus | 19 | 6 -82 43 & -3 -85 40 | 39 | 4.04 | .033 |

***Main effect of CU***

In the full sample, adolescents with High CU showed significantly greater BOLD responses in the right ventral striatum compared to adolescents with Average CU, see Table 25 and Figure 16.

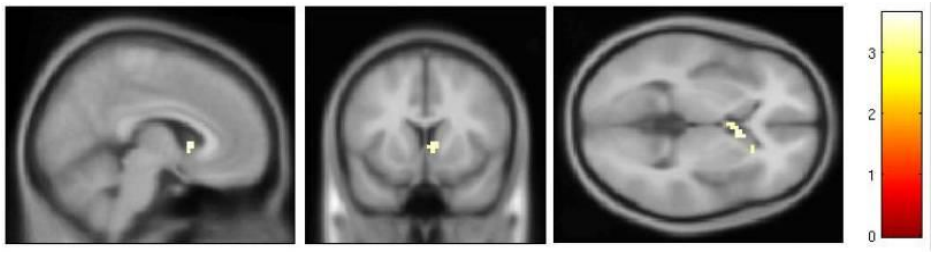


Figure 16 Whole Brain Analysis Emotional Reactivity Task: High CU > Average CU

***Gender-by-CU Interaction***

There was a significant Gender-by-CU interaction in a sub-cortical cluster of the basal ganglia. The cluster appeared largely as white matter (Fornix) and also stretched into the ventricle, however a small portion stretched into the caudate (*xyz:* -5, 10, 6), see Figure 17. The beta values for the cluster were extracted and plotted to establish the direction of the interaction. In females, those who had High CU showed significantly greater BOLD responses compared to females with Average CU ($p<.001$). Females with High CU also showed significantly greater BOLD responses compared to Males with High CU, see Figure 18. In males reactivity in this cluster did not vary according to CU trait.

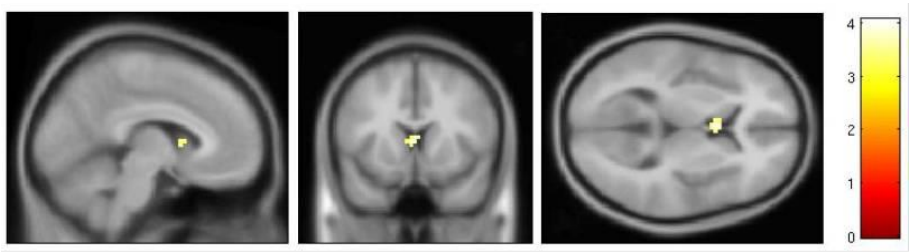


Figure 17 Whole Brain Analysis Emotional Reactivity Task: Gender-by-CU Interaction

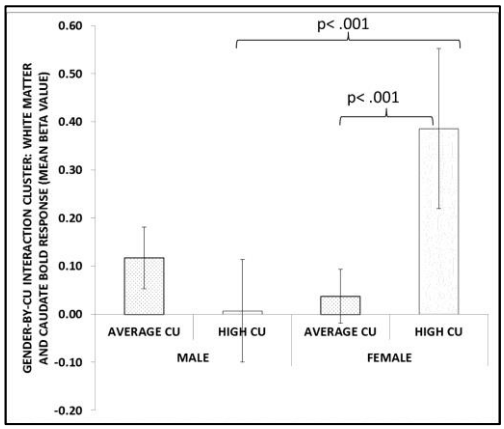


Figure 18 Whole Brain Analysis Emotional Reactivity Task: Gender-by-CU Interaction Plot (error bars 95% CI)

***Group-by-CU Interaction***

There was a significant Group-by-CU interaction in a cluster that included the cuneus and precuneus, see **Figure 19**. Within the CD group there was a significant effect of CU trait. The CD adolescents with High CU showed significantly greater hypoactivation of the cuneus/precuneus cluster compared to CD adolescents with Average CU ($p$<.001), see Figure 20. In control adolescents reactivity did not vary according to CU trait.

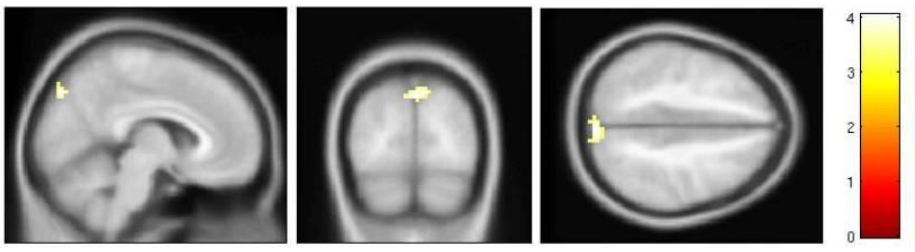


Figure 19 Whole Brain Analysis Emotional Reactivity Task: CD-by-CU Interaction in the Cuneus/Precuneus

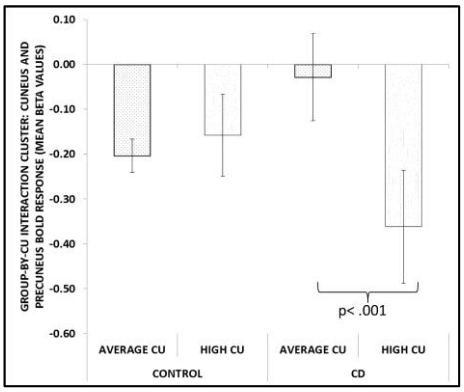


Figure 20 Whole Brain Analysis Emotional Reactivity Task: Group-by-CU Interaction Plot (error bars 95% CI)

## 4.5 **Discussion**

*This study investigated neural reactivity to angry faces in males and females with CD problems and explored the extent to which gender and callous-unemotional traits further moderated reactivity. There was a significant Gender-by-Group interaction at the region of interest level (amygdala). Consistent with expectation males with CD showed the lowest level of neural reactivity in the right amygdala; however in females there was no difference in amygdala reactivity between CD groups. The exploratory whole brain analysis revealed significant differences in neural reactivity of males and females, and also as a function of CU trait. There was significantly greater activation in the right caudate in adolescents with High CU. There was also significant activation of the left caudate in females with High CU compared to females with Average CU, however there was no effect in males. Finally there was a significant Group-by-CU interaction; the CD group with High CU showed significantly greater hypoactivation of the cuneus/precuneus compared to the CD group with average CU. There were no significant effects in control participants as a function of CU.*

***Gender-by-Group Interaction: Males with CD showed significantly lower BOLD response in the Amygdala compared to Control Males***

Consistent with the findings of Fairchild *et al.,*(2009), adolescents with CD showed reduced, rather than increased, responses to angry faces, although this effect was sex-specific and only affected males. In females, amygdala response did not vary according to group at the whole brain or region of interest level of analysis, despite females with CD showing comparable levels of CD symptoms as the males.

This finding is interesting as emotional expressions give clear signals as to the feelings and intentions of other people. Angry faces are a salient social signal of punishment indicating the individual should cease their current behaviour. One possible hypothesis underlying this effect might be to do with socio-emotional learning. Amygdala activity to both positive and negative stimuli reflects "the quick identification of salient stimuli in the environment and the production of adaptive behavioural and physiological responses" (Fossati, 2012). Individuals with CD have difficulty learning from punishment, an effect that was discussed in section 1.5 of the introduction, and this effect may not be limited to behavioural paradigms examining risk taking and decision making, but may also affect emotional learning. Animal studies have suggested that the amygdala is important for the formation of stimulus-reinforcement associations (Everitt, Cardinal, Parkinson, & Robbins, 2003). Therefore one might hypothesise that if amygdala response is blunted, or reduced, in response to social signals of punishment, then it might mean that the association between the particular emotion and the appropriate outcome are never made. This could explain why children and adolescents with CD continue to behave badly despite being reprimanded; it may be that the association between behaviour and outcome were not initially formed correctly. It is possible that males and females might have different developmental routes to CD problems, perhaps males with CD have a neural vulnerability for the development of aberrant emotion processing while females develop the

symptoms of CD as a function of environmental influences, which is why the same pattern of reactivity is not observed in females.

***Main effect of gender; whole brain analysis***

Consistent with previous reports, this task activated areas of the brain known to be involved in processing faces and faces with angry expressions (Fusar-Poli *et al.,*2009; Schneider *et al.,*2011). At the whole brain level males showed stronger activation in the medial prefrontal cortex, paracingulate gyrus, precuneus and posterior cingulate gyrus compared to females, while females showed significantly greater activation in a distributed set of regions including the fusiform gyrus, inferior temporal gyrus, inferior frontal gyrus, supramarginal gyrus and the occipital cortex.

Preferential activation of the medial prefrontal cortex at the whole brain level in males compared to females is of particular interest. The medial prefrontal cortex is a social brain region involved in the attribution of mental states (Castelli, Happe, Frith, & Frith, 2000), emotion processing generally (Phan, Wager, Taylor, & Liberzon, 2002), and the evaluation of one's own emotional experience (Ochsner *et al.,*2004). Activation of the mPFC and amygdala are proposed to underlie the control of emotional reactions through the strength of their functional co-activation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007), particularly in response to negative emotions; "dynamic interactions between the amygdala and the medial prefrontal cortex (mPFC) are usefully conceptualized as a circuit that both allows us to react automatically to biologically relevant predictive stimuli as well as regulate these reactions when the situation calls for it" (Kim *et al.,*2011). It is possible that the males in this study were overall more sensitive to angry faces than females, and showed more activation in the mPFC as it took more neural resources for them to monitor their own emotional state in response to

the stimuli. This finding is in line with previous studies. In a recent review of sex differences in emotion processing Kret and De Gelder (2012) presented evidence that males show greater responses compared to females and suggested that emotional stimuli could provide different kinds of 'behaviourally relevant cues' to males compared to females that result in different behavioural outcomes due to innate differences in the biological fight or flight response.

***Callous Unemotional Traits***

There were three interesting effects associated with callous unemotional traits; a significant main effect of CU in the basal ganglia, a Gender-by-CU interaction in a small part of the caudate and a significant Group-by-CU interaction in the cuneus and precuneus. The main effect of CU and the Gender-by-CU interaction effects are discussed together first. There is evidence to suggest that the striatum is strongly linked to the processing of rewards (see Knutson *et al.,*2000), and its more ventral portion is also important for the recognition or coding of anger (Calder, Keane, Lawrence, & Manes, 2004). High CU traits are associated with a dominant behavioural style, therefore the angry stimuli might be interpreted as a social challenge or provocation by the individuals in this study with High CU resulting in a larger neural response (discussed in Calder, Ewbank & Passamonti, 2011). This would make sense as facial signals of aggression usually provoke a negative reaction in the viewer.

This notion is plausible, individuals with High CU traits do show more aggressive behaviours compared to their peers. There is also an additional sex-specific effect in the left caudate in females with High CU who show significantly greater neural responses compared to females with Average CU, and also compared to males with High CU. It is possible that females with High CU may be generally more sensitive to negative stimuli. The results presented earlier in this thesis suggest that High CU in females is associated with greater symptoms of emotional problems and hopelessness. This effect in females might therefore be associated with their

negative interpersonal style which manifested as a hypersensitivity to negative socially reinforcing stimuli (angry faces).

A second significant Group-by-CU interaction effect was observed in a cluster including the cuneus and precuneus. Individuals with CD problems and High CU showed significantly greater hypoactivation in this area compared to individuals with CD problems and only Average levels of CU. Hypoactivation of these regions adds to the data available that CD with CU shows altered neural processing during presentation of emotional stimuli. There is evidence to suggest that the precuneus is involved in self and other oriented judgements (Ochsner *et al.,*2004) and may be important for the attribution of one's own or indeed others' feelings. In terms of the effect observed in this study the hypoactivation of these regions may reflect the blunted emotional affect characteristic of this group.

***Limitations***

One limitation of this study was the lack of a range of emotional stimuli, only ambiguous and angry faces were included in the experimental paradigm. Anger is an unambiguous emotion that provides information about the source of threat however it is possible the ambiguous faces used in this paradigm were perceived as non-neutral as evidenced by the significant response in the amygdala, see Appendix Chapter 4. Consequently this study examined the angry versus control circles contrast. It would have been preferable to have contrasted the activation associated with processing angry faces with a less ambiguous more neutral face which would have resulted in regions associated specifically with the processing of angry emotional stimuli, rather than face processing more generally. In addition it would have been preferable to include a range of positive and negative emotions to comprehensively explore the patterns of reactivity in males and females with and without CD problems and CU traits.

***Conclusions***

This chapter described how patterns of neural reactivity in response to angry faces varied as a function of gender, group and CU traits. Consistent with previous reports this study provides evidence that CD problems are associated with reduced activations in the amygdala in response to anger in males. This study also provides new evidence that females and males with High CU traits might process negative emotional information in different ways, and discussed the possibility that females may show a heightened response to negative social reinforcement.

# Chapter 5 Cool Executive Function

*This study investigated the extent to which adolescents with conduct disorder problems showed difficulties with measures of cool executive function ability using a battery of neuropsychological tasks, and explored the neural mechanisms of inhibitory control using a Stop Signal fMRI paradigm. The extent to which cool executive function deficits prevailed in conduct disorder and the extent to which these difficulties differ in males and females and as a function of callous-unemotional traits were also explored.*

## 5.1 Introduction

***What is Executive Function?***

Executive function (EF) is a term applied to the multi-faceted range of higher order abilities used to monitor and adjust behaviour. Self-control and self-monitoring, planning, selective attention, working memory, task switching, decision making and inhibition are all examples of executive function abilities. In a review of the EF literature Jurado and Rosselli (2007) reported that the concept of EF was initially defined by Baddeley and Hitch (1974) and then again by Lezak (1983) as "the dimension of behaviour that deals with how behaviour is expressed". Jurado and Rosselli, (2007) also asserted that the different facets of executive function are all necessary for "appropriate, socially responsible and effectively self-serving adult conduct". This suggests that if any one of these processes is disrupted then this could be detrimental for the individual. EFs allow people to adapt their behaviours to new rapidly changing circumstances and crucially to inhibit inappropriate behaviours. This chapter is concerned with 'cool' EF; those processes thought to be more cognitive in nature, so those not associated with an emotional or motivational drive. There are a number of facets of cool EF however this chapter will deal with two aspects; inhibitory control (the cessation of actions) and working memory.

*Inhibitory Control*

Inhibitory control is an important facet of EF as it allows the individual to focus on the task at hand and to block out other sources of interference, enabling them to complete a task as efficiently as possible. Methods for assessing inhibitory control are the Go/No-Go or Stop Signal task paradigms. In the Stop Signal task the individual is taught to respond to a 'go' stimulus by making a button press whenever the stimulus is shown. A minority of trials contain a 'stop signal' displayed shortly after the 'go' stimulus to which he/she has been responding to. Inhibitory control is measured by the success or failure of the individual to suppress their responses when the stop signal is presented. This simple task means that one can take an accurate measure of performance and make an inference about the degree to which an individual has intact or disrupted EF in terms of inhibitory control.

*Working Memory*

Working memory refers to the ability to keep information 'online' or consciously represented while it is being worked on during a task, for example, recalling a sequence of digits in the reverse order to which they were presented. Working memory allows the facilitation of many other EF behaviours, such as goal-directed behaviour, by enabling an individual to hold a goal in mind. If working memory ability is disrupted it might mean that the individual is unable to keep goals in mind and then their behaviour could be driven by immediate stimuli in the environment or by rewarded behaviour. Tasks examining working memory include digit span and spatial working memory and both employ sequential presentation of items or items to be recalled (e.g. shapes, counter location, numbers) over a delay period between items.

### *The Neural Basis of Cool Executive Function*

In a review of the literature Alvarez and Emory (2006) describe a region of the prefrontal cortex that projects primarily to the head of the caudate nucleus that has been linked to EFs such as verbal and design fluency, the ability to maintain and shift set, planning, response inhibition, working memory, organisational skills, reasoning, problem solving and abstract thinking.

### *Exploring the Neural Basis of Cool Executive Function using a Stop Signal Task*

This chapter used a stop signal fMRI paradigm to investigate the neural basis of inhibitory control. The task tests a 'race-model' (Schachar & Logan, 1990) that is, the race between stop and go-processes at a late stage of inhibition that requires "the effortful cancellation of a routine response when an infrequent stop cue is detected" (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). If the stop process wins then the individual has successfully inhibited their response, however if the go-process wins then inhibition has lost and there has been a stop-failure. The task is made more difficult by increasing the delay between the go-stimulus and stop-stimulus and is easier when the delay is shorter.

In a recent meta-analysis of the inhibitory control literature Swick, *et al*. (2011) identified a number of regions in the prefrontal cortex significantly activated by the action of successful stopping; a left insula cluster that extended into subcortical areas (thalamus and putamen) and the posterior cingulate, other major clusters were found in the right hemisphere and included the right insula, inferior and precentral gyri, superior and middle frontal gyri and the inferior parietal lobule. While the areas involved in successful inhibition are numerous, this study investigates just one region, the right inferior frontal gyrus and the reasoning behind this selection follows in the next section.

***The Right Inferior Frontal Gyrus: Candidate Brain Region of Interest***

The right inferior frontal gyrus (IFG) is one of the most strongly and consistently activated brain areas during successful response inhibition (stop-success). By 'active' this means that the blood oxygenation level dependent (BOLD) signal in the rIFG increases when participants are required to inhibit their responses compared to a baseline where they are not; see reviews by Aron, Robbins, and Poldrack (2004) and Garavan, Ross, and Stein (1999). In a recent study, Chevrier, Noseworthy, and Schachar (2007) found that response withdrawal prompted by the stop signal significantly activated the rIFG, and this was the only frontal structure associated with response inhibition when the authors controlled for go-processes. While the work of Hampshire and colleagues challenged the notion of rIFG uniqueness or specificity for response inhibition, the authors also found evidence for rIFG activation in response to the counting of cues, initiation of response and inhibition of responses (Hampshire *et al.,*2010).

The rIFG may therefore be considered a candidate brain region that plays a role in the mediation of impulsive behaviour. This notion has been recently investigated by a group of IMAGEN Consortium members who demonstrated that trait impulsivity was significantly associated with reduced rIFG grey matter volume (Schilling *et al.,*2013). Chapter Three of this thesis reported that adolescents with CD problems showed greater trait impulsivity compared to the Control group. As such this study focused specifically on the rIFG to (i) limit the number of corrections for multiple comparisons and (ii) because disrupted inhibitory control is potentially a core aspect of conduct disorder problems one would predict significant disruption in this area.

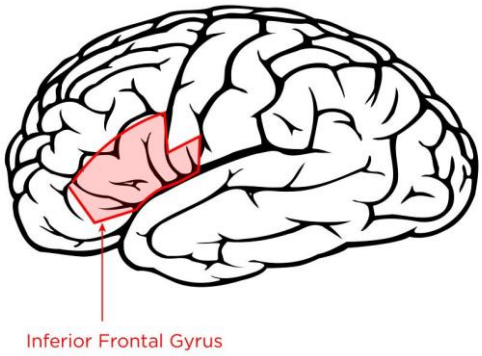


Figure 21 Approximate Anatomical Location of the Inferior Frontal Gyrus

***Disrupted Executive Function in Conduct Disorder***

There is some evidence to suggest that individuals with CD problems have difficulties monitoring and adjusting their behaviour, which could be a consequence of executive dysfunction. Studies have reported a range of impairments associated with CD problems such as lower general intelligence (Pajer *et al.,*2008), slower inhibitory processes during a stop task (Hobson, Scott, & Rubia, 2011; Herba, Tranah, Rubia & Yule, 2006), working memory deficits (Syngelaki *et al.,*2009; Barnett *et al.,*2009; Cauffman *et al.,*2005) more perseverative responses (Toupin *et al.,*2000) and more impulsive commission errors (van der Meer & van der Meere, 2004). Some of the evidence supporting the assertion of executive dysfunction in CD is presented in Table 26; however this table also presents evidence to suggest that individuals with CD show no executive function difficulties. These inconsistencies are perhaps a consequence of differences between the tasks used in each study.

An additional explanation for the inconsistencies reported in EF function in CD could be that differences in IQ between CD cases and control participants are not always adequately controlled. When differences in IQ are controlled for, any deficits in function or performance in clinical groups cannot be explained by known group differences in intelligence; this is

particularly pertinent for the CD groups where it is known that low IQ is significantly associated with the disorder (Pajer *et al.,*2008; Goodman, Simonoff, & Stevenson, 1995). An additional potential confounding variable is the overlap in aetiology between CD and Attention Deficit Hyperactivity Disorder (ADHD). As discussed in Chapter 2, section 0, researchers have found that there can be substantial overlap or co-morbidity between the two disorders in clinical (Biederman *et al.,*2006) and community samples (van Lier *et al.,*2003; Waschbusch, 2002). This overlap indicates that these disorders may have a shared aetiology. There is a large body of evidence to suggest that individuals with ADHD also have difficulty with executive function tasks, especially those investigating inhibitory control (Rubia *et al.,*2001), but also spatial working memory, set-shifting and visual information processing (Fried, Hirshfeld-Becker, Petty, Batchelder, & Biederman, 2012). This suggests that when investigating executive function ability in individuals with CD one must also investigate how co-occurring symptoms of ADHD might influence the results.

Table 26 Summary of Findings: Cold Executive Dysfunction in CD ± CU or Psychopathy

| Authors | Task | Age Group | Sample | Gender | Comparison | Finding |
|---|---|---|---|---|---|---|
| Toupin, Dery, Pauze, Mercier & Fortin (2000) | WCST | 7-12 | Clinical<br>CD (n57) Control (n35) | M & F | CD > Control | More Perseveration Errors |
| van der Meer & van der Meere (2004) | Response Inhibition | 10-13 | CD (n21) Control (n18)<br>Borderline Intellectual Function (BIF) (n19) | Male | CD > BIF | More Commission Errors (poor impulse control) |
| Syngelaki, Moore, Savage, Fairchild & Van Goozen (2009) | CANTAB Spatial Working Memory<br>WCST | 12-18 | Offenders (n104) | Male | Offenders > Control | Perseveration Errors<br>Between Search Errors<br>Inefficient Strategy |
| Schoemaker, Bunte, Wiebe, Espy, Dekovic & Matthys (2012) | Working Memory<br>Inhibition | 3.5 - 5.5 | ADHD (n61) DBD (n33) ADHD+DBD (n52)<br>Controls (n56) | M & F | No Effects<br>ADHD, ADHD+DBD, DBD > Control | Working Memory no impairment<br>Inhibition |
| Pajer, Chung, Leininger, Wang, Gardner & Yeates (2008) | General Intelligence<br>WCST | 15-17 | CD (n52)<br>Control (n41) | Female | Control > CD<br>CD > Control | IQ<br>Perseveration Errors |
| Barnett, Maruff & Vance (2009) | Spatial Working Memory | 6-12 | ADHD (n23) ADHD+ODD (n22) ADHD+CD (n20) Controls (n25) | M & F | Control > ADHD, ADHD+ODD, ADHD+CD<br>ADHD, ADHD+ODD, ADHD+CD > Control | Spatial Span<br>SWM Between Search Errors |

| Authors | Task | Age Group | Sample | Gender | Comparison | Finding |
|---|---|---|---|---|---|---|
| Cauffman, Steinberg & Piquero (2005) | CANTAB SWM | 14-19 | Offenders (n105) Controls (n78) | M & F | Offenders > Controls & F > M | Inefficient Strategy |
| | CANTAB Spatial Span | | | | Controls > Offenders M > F | Spatial Span |
| Clark, Prior & Kinsella (2000) | Six Elements Test | 12-15 | ADHD (n35) ADHD+ODD/CD (n38) ODD/CD (n11) Controls (n26) | M & F | Control > ADHD, ADHD+ODD/CD | Errors specific to ADHD groups not as a function of ADHD/CD |
| Dery, Toupin, Pauze, Mercier, and Fortin (1999) | WCST | 13-17 | ADHD+CD (n14) CD (n45) Control (n29) | M & F | No significant effects | No significant effects |
| | Stroop | | | | | |
| Dolan & Lennox (2013) | SOC | 13-18 | ADHD+CD (n35) CD (n72) Control (n20) | Male | Controls, CD > CD+ADHD | Problem Solving |
| | ID/ED | | | | | Set-Shifting Tasks |
| | Go/No Go | | | | No significant differences | Response Inhibition |
| | | | | | No significant differences | |
| Dougherty, Bjork, Harper & Marsh (2003) | IMT/DMT | 13-17 | Inpatients with DBDs (n22) Controls (n22) | M & F | DBDs > Controls | Immediate Memory Task |
| | | | | | DBDs > Controls | Delayed Memory Task |
| | Go/No Go Task | | | | Control > DBDs | Inhibited response rate in stop trials |

| Authors | Task | Age Group | Sample | Gender | Comparison | Finding |
|---|---|---|---|---|---|---|
| Lueger & Gill (1990) | WCST<br>SMMT | 13-17 | CD (n21) Controls (n20) | Male | CD > Control<br>CD > Controls | Perseverative responses and errors<br>Memory errors |
| Herba, Tranah, Rubia & Yule (2006) | Inhibition (motor, verbal, cognitive) | 14-16 | CD (n54) Control (53) | M & F | No significant differences<br>Control > CD (inefficient)<br>CD > Control | Stop signal Reaction Time<br>Inhibitory Control<br>Premature Responses |
| Hobson, Scott & Rubia (2011) | Go/No-Go<br>Continuous Performance Task (CPT)<br>Iowa Gambling Task (IGT) | 10-17 | CD/ODD (n28) ADHD+CD/ODD (n31) Controls (n34) | M & F | Control > CD (inefficient)<br>CD > Control<br>CD > Control | Slower inhibition<br>Omission and Commission Errors<br>Premature Errors |

Disruptive Behaviour Disorders (Conduct Disorder, CD; Oppositional Defiant Disorder, ODD; Attention Deficit Hyperactivity Disorder, ADHD); Wisconsen Card Sorting Test (WCST) Perseveration Errors; failure to modify responses based on a new task criterion; Commission errors; poor impulse control, failure to appropriately inhibit response to a given cue; Omission Errors; failure to respond to a given cue; Sequential memory matching task (SMMT); Continuous performance test (CPT) Between-search errors; returning to a position where a target has already been located; Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM); Stockings of Cambridge (SOC); Intra-Dimensional/Extra-Dimensional set -shifting tasks (ID/ED); Immediate Memory Task (IMT)/ Delayed Memory Task (DMT); a modified continuous performance test

***Hypotheses and Predictions***

This study explored the notion that adolescents with CD problems experience executive function difficulties in working memory using well validated neuropsychological tests; the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory task and Wechsler Intelligence Scale for Children (WISC) Digit Span sub-test (reverse). It was predicted that the CD group would show significantly greater working memory deficits compared to the control group in the following ways; (i) they would make more errors in their searches (Between-Errors) and (ii) would use a less efficient search strategy in the spatial working memory task and (iii) would have a more limited short term memory evidenced by a shorter digit span recall.

In terms of inhibitory control it was predicted that adolescents with CD would show significantly worse inhibitory control ability compared to the control group by (i) making more premature responses and (ii) a shorter reaction time to stimuli in the Stop Signal Task. In terms of neurofunctional reactivity it was expected that the CD adolescents would need to exercise more effort in the inferior frontal gyrus to control their impulses which would be evidenced by a significantly larger BOLD response in the stop-success contrast compared to controls.

There was no expectation that these effects would vary according to gender; previous work has suggested that females with CD problems also experience difficulties in working memory and inhibitory control. There was also no expectation that callous unemotional traits would be associated with any particular advantage or disadvantage in terms of spatial working memory or response inhibition; none of the studies cited in Table 26 investigated the extent to which these abilities varied according to CU. This is perhaps a consequence of CU traits being more readily associated with difficulties processing rewarding and punishing stimuli which are more related to 'hot' EF. Nevertheless, this trait was investigated to be consistent with the other studies in this thesis.

An additional aim of this study was to explore the extent to which verbal IQ and symptoms of hyperactivity/inattention accounted for significant between-group differences, thus three statistical models were investigated.

## 5.2 **Method**

***Participants***

Participants with Conduct Disorder Problems (CD) were those classed as 'possible' or 'probable' CD cases (N=163) according to the Strengths and Difficulties Questionnaire (SDQ). All participants classed as 'unlikely' to develop CD are referred to as Controls (N=857). Adolescents with 'High CU' were those who scored more than one standard deviation above the mean (a score of 7 or more; N=176), the 'Average CU' group were those who scored between 0-6 points (N=844), for further information on both these criteria pleases see Chapter 2, section2.2.

Group characteristics (mean, standard deviation) for demographic variables may be found in Table 24 and Table 28 and full test statistics in Appendix Chapter 5, Table 64 and Table 65. There were two main effects on verbal IQ; Group: $F(1,1007)$ 14.28, $p<0.001$, eta²0.014 and Gender: $F(1,1007)$ 4.04, $p<0.05$, eta²0.014. The controls had a higher verbal IQ compared to the CD group and males had a higher verbal IQ compared to females. There were also two main effects on Hyperactivity/Inattention symptoms; Group: $F(1,1007)$ 110.63, $p<0.001$, eta²0.099, and Gender: $F(1,1007)$ 5.39, $p<0.05$ eta²0.005. The CD group had higher symptoms compared to controls, and males had more symptoms than females.

Table 27 Descriptive Statistics: Demographic Variables for Chapter Five [Males Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=41)** | **Average CU (N=56)** | **High CU (N=94)** | **Average CU (N=313)** |
| Age | 14.40 (0.44) | 14.44 (0.37) | 14.37 (0.41) | 14.41 (0.39) |
| Verbal IQ | 111.37 (16.51) | 109.25 (14.91) | 115.56 (16.79) | 113.24 (13.42) |
| Performance IQ | 108.10 (16.67) | 106.16 (13.32) | 108.79 (14.96) | 109.71 (13.55) |
| Hyperactivity/Inattention | 4.88 (2.79) | 4.88 (2.59) | 3.06 (2.14) | 2.72 (2.02) |

Table 28 Descriptive Statistics: Demographic Variables for Chapter Five [Females Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=14)** | **Average CU (N=52)** | **High CU (N=27)** | **Average CU (N=423)** |
| Age | 14.33 (0.36) | 14.43 (0.47) | 14.45 (0.38) | 14.41 (0.41) |
| Verbal IQ | 108.64 (18.4) | 105 (16.61) | 111.96 (14.18) | 111.22 (14.25) |
| Performance IQ | 110.5 (10.07) | 103.65 (14.88) | 108.52 (12.98) | 108.32 (13.98) |
| Hyperactivity/Inattention | 4.57 (2.38) | 4.54 (2.01) | 2.15 (1.68) | 2.17 (1.89) |

Participants with complete data that passed fMRI task specific outlier criteria in terms of movement, spike detection, were able to view the task stimuli without obstruction and did not show anatomical abnormalities were included in the analysis. Individuals with good neuropsychological data and behavioural measures from the SST were also included. In total N=1020 individuals had full datasets for the SST Inferior Frontal Gyrus region of interest and CANTAB SWM measures, of that total, N=1017 had information for the WISC Digit span measure, N=899 had behavioural premature response data and N=551 had reaction time data from the SST. Due to a problem with the tracking algorithm data were not available for the full cohort for the SST. The problem was that if the subject responded prior to a stop stimulus appearing on a stop trial then that trial was repeated once (a maximum of seven such trials; stop- too-early trials, were repeated). This may have affected the reaction time data as some

subjects had more stop-too-early trials than others. Where there were subjects who had more than eight stop-too-early trials the reaction time data were calculated up to the point of the eighth trial, but for some subjects this happened early during the task. The reaction time data were calculated for all subjects who did not reach this eighth stop too early threshold before their 300$^{th}$ trial. The reaction time data were calculated by Dr Robert Whelan and Professor Hugh Garavan at the University of Vermont and made available for the members of the IMAGEN consortium to download.

***Materials and Procedures***

*Standardised Assessment Tools*

Spatial working memory was measured using the CANTAB, for task details please see Chapter Two, section 2.2. Two dependent variables were used; Between-Error Score and Strategy Score. Between-Errors were defined as the number of times a subject returned to a box in which a token had previously been found; a high score indicated worse performance. The Strategy Score estimated how efficient the participant's searches were by counting the number of times a search began with a new box (after a token had been found). A high score indicated a poor use of strategy.

Short term memory store was measured using the Digit Span subtest of the WISC please see Chapter Two, section 2.2, and used the maximum number of digits recalled backwards as the dependent variable.

Behavioural measures of inhibition were taken from the Stop Signal fMRI paradigm, the dependent variables were reaction time and the number of premature responses made, see

Chapter Two, section 2.3 for a description of the task. The neuropsychological tasks were administered as part of the Institute visit; see Chapter Two,

All neuropsychological dependent variables were computed under the guidance of Dr Frauke Nees at the Central Institute of Mental Health in Mannheim and were made available for members of the IMAGEN consortium to download.

***fMRI Paradigm***

The Stop Signal Task was adapted from Rubia, *et al.* (2005) and Rubia, *et al*. (2007). Participants were required to respond to visually presented go or stop stimuli, for a detailed description of the task see Chapter Two, section 2.3. This study focused on stop success; that is all the trials during the task that the adolescents were able to successfully inhibit their response to the stop signal. The neuroimaging task was administered as part of a larger battery during the first of two imaging acquisition sessions; as described in Chapter Two, section 2.3.

***fMRI Data Acquisition and Analysis***

Structural and functional MRI data were acquired at eight IMAGEN assessment centres with 3T MRI scanners of different manufacturers, as described in Chapter Two sections 2.3. In the second level analysis a one sample t-test was used to identify brain regions that showed significant activation in trials when the adolescents successfully stopped their response. Summary statistical maps were thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for gender, site and handedness.

*Region of Interest (ROI) Analyses*

The right inferior frontal gyrus ROI was extracted using the MARSBAR toolbox (http://marsbar.sourceforge.net) based on the Montreal Neurological Institute (MNI) Automated Anatomical ROI. The beta values for responses during stop-success were averaged across all voxels within the ROI using the MarsBar toolbox and the data exported for group-level analyses in SPSS.

***Data Analysis***

All analyses (neuropsychological and ROI) were conducted using SPSS V.20. Analyses of covariance (ANCOVA) were conducted using the General Linear Model. Independent factors included Group (CD vs. Control), gender and CU (High vs. Average). Interactions between the factors were explored and two- and three-way interactions were modelled. The full model was examined first in each instance to include all main and interaction effects. Where the 3-way interaction was not significant the term was removed from the model so that the 2-way interactions could be better investigated. To account for local differences in recruitment strategy, and between-site differences in fMRI scanner, site was controlled for in all analyses. For all imaging analysis handedness (left/right/ambidextrous) was additionally controlled for.

*Covariates*

Due to significant associations between verbal IQ and Hyperactivity/Inattention and the outcome variables of interest (see Table 29), the known differences in verbal IQ ability between CD and control groups, and symptom overlap between CD and ADHD discussed in Chapter One (see section 2.4), three models were explored in this study. The first included site and gender (where appropriate) as covariates. The second model controlled for verbal IQ to ensure that any significant between-group differences were not a consequence of lower

average Verbal IQ in the CD group. The third model controlled for both verbal IQ and symptoms of Hyperactivity/Inattention to ensure that between-group differences were not due to the overlap in symptomology in CD and ADHD.

Table 29 Correlation Coefficients between Executive Function Variables, Verbal IQ and Hyperactivity/Inattention Symptoms (controlling for site)

| | **Verbal IQ** | | | | | |
|---|---|---|---|---|---|---|
| | **Full Sample** | | **Males** | | **Females** | |
| **Measure** | ***r*** | ***df*** | ***r*** | ***df*** | ***r*** | ***df*** |
| SST Premature Responses | -0.15*** | 891 | -0.15** | 436 | -0.15*** | 447 |
| Stop Signal Reaction Time | -0.01 | 543 | -0.02 | 254 | -0.02 | 281 |
| SWM Between-Errors | -0.22*** | 1012 | -0.24*** | 496 | -0.19*** | 508 |
| SWM Strategy Score | -0.19*** | 1012 | -0.23*** | 496 | -0.14** | 508 |
| WISC DSLB | 0.26*** | 1009 | 0.25*** | 494 | 0.27*** | 507 |

***$p$<0.001, **$p$<0.01, *$p$<0.05

| | **Hyperactivity/Inattention Symptoms** | | | | | |
|---|---|---|---|---|---|---|
| | **Full Sample** | | **Males** | | **Females** | |
| **Measure** | **r** | ***df*** | **r** | ***df*** | **r** | ***df*** |
| SST Premature Responses | 0.13*** | 890 | 0.14** | 436 | 0.13** | 447 |
| Stop Signal Reaction Time | 0.05 | 543 | 0.06 | 254 | 0.02 | 281 |
| SWM Between-Errors | 0.17*** | 1012 | 0.19*** | 496 | 0.17*** | 508 |
| SWM Strategy Score | 0.11*** | 1012 | 0.14** | 496 | 0.11* | 508 |
| WISC DSLB | -0.10*** | 1009 | -0.05 | 494 | -0.14** | 507 |

***$p$<0.001, **$p$<0.01, *$p$<0.05

SST: Stop Signal Task

WISC: Wechsler Intelligence Scale for Children

DSLB: Digit Span Longest Backwards

SWM: Spatial Working Memory

## 5.3 **Results: Neuropsychological Measures**

***Neuropsychological and Behavioural SSRT Measures***

See Table 30 and

Table 31 for descriptive statistics and Table 66 - Table 72 in Appendix Chapter 5 for test statistics. Table 32 details the significant main and interaction effects from these analyses.

Table 30 Descriptive Statistics Cool Neuropsychological Measures [Males Mean (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| **Measure** | **High CU (N=41)** | **Average CU (N=56)** | **High CU (N=94)** | **Average CU (N=313)** |
| SST Premature Responses | 15.32 (8.21) | 12.10 (8.39) | 12.70 (8.88) | 12.31 (8.83) |
| SSRT(ms) | 236.61 (47.49) | 223.86 (28.49) | 221.19 (39.43) | 223.21 (40.46) |
| WISC DSLB | 5.05 (1.32) | 4.88 (1.24) | 5.18 (1.29) | 4.84 (1.22) |
| SWM Between-Errors | 21.24 (11.07) | 21.21 (15.12) | 16.82 (12.35) | 17.25 (12.40) |
| SWM Strategy Score | 31.88 (3.76) | 31.66 (5.19) | 30.47 (5.25) | 30.02 (5.60) |

Table 31 Descriptive Statistics Cool Neuropsychological Measures [Females Mean (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| **Measure** | **High CU (N=14)** | **Average CU (N=52)** | **High CU (N=27)** | **Average CU (N=423)** |
| SST Premature Responses | 16.85 (11.82) | 13.82 (9.25) | 11.16 (5.96) | 11.75 (8.69) |
| SSRT(ms) | 205.21 (53.36) | 226.14 (35.34) | 223.54 (21.67) | 218.76 (33.65) |
| WISC DSLB | 4.79 (1.19) | 4.58 (1.13) | 4.96 (1.40) | 4.98 (1.28) |
| SWM Between-Errors | 23.14 (15.11) | 24.98 (16.38) | 18.37 (15.31) | 18.39 (13.83) |
| SWM Strategy Score | 30.07 (5.55) | 32.69 (5.11) | 31.33 (4.10) | 31.07 (5.45) |

Table 32 Summary of Significant Main and Interaction Effects Cool Neuropsychological Tasks

| **Interactions** | **Group-by-CU-by-Gender** | | | **Group-by-CU** | | | **Group-by-Gender** | | | **Gender-by-CU** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** |
| SST Premature Responses | × | × | × | × | × | × | × | × | × | × | × | × |
| SSRT(ms) | ✓ | ✓ | ✓ | × | × | × | × | × | × | × | × | × |
| WISC DSLB | × | × | × | × | × | × | × | × | × | × | × | × |
| SWM Between-Errors | × | × | × | × | × | × | × | × | × | × | × | × |
| SWM Strategy Score | × | × | × | × | × | × | × | × | × | × | × | × |

| **Main Effects** | **Group** | | | **CU** | | | **Gender** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** |
| SST Premature Responses | ✓ | ✓ | × | × | × | × | × | × | × |
| SSRT(ms) | × | × | × | × | × | × | × | × | × |
| WISC DSLB | × | × | × | × | × | × | × | × | × |
| SWM Between-Errors | ✓ | ✓ | ✓ | × | × | × | × | × | × |
| SWM Strategy Score | ✓ | × | × | × | × | × | × | × | × |

***Main effect of Group***

There was a main effect of group across all three models for the CANTAB Spatial Working Memory Variable "Between-Errors". Adolescents with CD made significantly more errors than the controls. This means the CD group returned more frequently to a box where a token had previously been found, despite being instructed not to. There was also a main effect for group in terms of Spatial Working Memory "Strategy Score". The CD group made significantly less efficient searches compared to controls; however this effect was not significant following correction for between-group differences in verbal IQ (Model 2). There were no significant main effects or interactions for the digit span subtest of the WISC.

There was a significant main effect for one of the behavioural measures of the SSRT. CD adolescents made significantly more premature response errors compared to controls even when verbal IQ was controlled. However, controlling for both verbal IQ and symptoms of hyperactivity/inattention eliminated the significant between-group differences.

***Gender-by-Group-by-CU Interaction***

There was a significant interaction for the SSRT measure; however the significant effects did not remain after correction for multiple comparisons. There were no other significant main effects or interactions for these variables.

## 5.4 **Results: fMRI Paradigm: Stop Signal Task**

***Random Effects Analysis***

A one sample t-test was performed to identify brain regions significantly activated in the Stop-Success contrast. Summary statistical maps were thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for gender, site and handedness. Consistent with previous reports (Swick *et al.,*2011) there were significant activations across the prefrontal cortex including the right inferior frontal gyrus, superior and middle frontal gyri and anterior cingulate gyrus. Additionally there were significantly active regions in the parietal lobe (superior parietal lobule and supramarginal gyrus). This was consistent with findings of (Collette *et al.,*2005) who suggested that parietal areas play a critical role during the performance of executive tasks, and are required to execute basic attentional processes needed for good executive performance. See Table 33 and Figure 22.

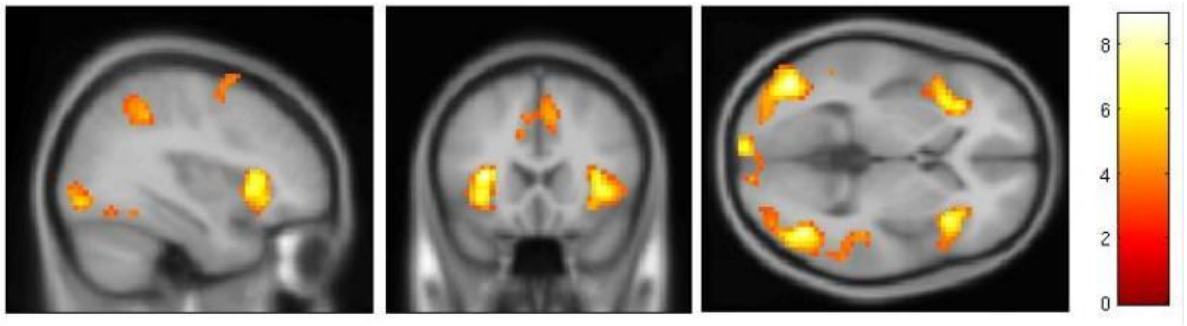


Figure 22 Random Effects Clusters for the Stop Signal Task 'Stop Success' Contrast (Full Sample)

Table 33 Significant Random Effects Clusters for the Stop Signal Task 'Stop Success' Contrast (Full Sample)

| **Full Sample Random effects analysis** | | | | | **Cluster** |
|---|---|---|---|---|---|
| **Brain Region of Activation (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Insula, Orbitofrontal Cortex | 13 | -33 17 7 | 225 | Inf | $1.73^{-8}$ |
| Bilateral Occipital Cortex | | -45 -73 1 | 1740 | Inf | <0.001 |
| Insula, Inferior Frontal Gyrus | | 36 20 1 | 220 | 7.27 | $2.38^{-8}$ |
| Superior Frontal Gyrus, Middle Frontal Gyrus, Precentral Gyrus | 6 | -24 -4 52 | 45 | 5.43 | 0.018 |
| Paracingulate Gyrus, Anterior Cingulate Gyrus, Superior Frontal Gyrus | 6, 24 | 9 32 31 | 217 | 5.43 | $2.86^{-8}$ |
| Middle Temporal Gyrus, Angular Gyrus, Supramarginal Gyrus | | -48 -52 7 | 40 | 5.31 | 0.030 |
| Superior Parietal Lobule, Supramarginal Gyrus | 40 | -36 -43 40 | 81 | 5.13 | 0.001 |
| Middle Frontal Gyrus, Precentral Gyrus, Superior Frontal Gyrus | 6 | 30 -1 52 | 106 | 4.76 | $6.97^{-5}$ |
| Supramarginal Gyrus | 40 | -51 -46 61 | 44 | 4.51 | 0.020 |

Clusters include peaks that are significantly active that include the regions listed under brain region of activation.

***Region of Interest Analysis***

As the inferior frontal gyrus in the right hemisphere was the only region selected for analysis, the statistical threshold was set at $p<0.05$. See Table 34 for the descriptive statistics, test statistics may be found in Appendix Chapter 5, Table 73. Table 35 details the significant main and interaction effects from these analyses.

Table 34 Descriptive Statistics for the Stop Signal Task Contrast 'Stop Success' Region of Interest Right Inferior Frontal Gyrus: Mean Beta Values (SD)

| | **Male** | | **Female** | |
|---|---|---|---|---|
| | **CD (N=97)** | **Control (N=407)** | **CD (N=66)** | **Control (N=450)** |
| **rIFG** | .58 (1.37) | .32 (1.23) | .01 (1.31) | .25 (1.13) |

Table 35 Summary of Significant Main and Interaction Effects Stop Signal fMRI Paradigm

| **Interactions** | **Group-by-CU-by-Gender** | | | **Group-by-CU** | | | **Group-by-Gender** | | | **Gender-by-CU** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** |
| r IFG | × | × | × | × | × | × | ✓ | ✓ | ✓ | × | × | × |

| **Main Effects** | **Group** | | | **CU** | | | **Gender** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Model** | **1** | **2** | **3** | **1** | **2** | **3** | **1** | **2** | **3** |
| r IFG | × | × | × | × | × | × | × | × | × |

***Gender-by-Group Interaction***

There was a significant Gender-by-Group interaction in the IFG. Within the CD group, CD Males showed significantly greater rIFG response compared to CD Females. Within the Control group there was no significant difference between rIFG response in males and females ($F(1,846)$ 0.26, $p>.05$), see Figure 23 and

Table 36 for post-hoc comparisons for each model. There were no other significant main effects or interactions.

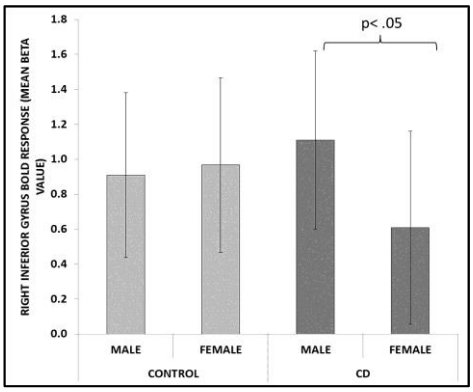


Figure 23 Region of Interest Analysis: Significant Gender-by-Group Interaction for the Stop Signal Task 'Stop Success' Contrast in the Right Inferior Frontal Gyrus (adjusted for IQ and Hyperactivity/Inattention Symptoms, error bars 95% CI)

There were two instances where SST behavioural data were reduced. In the first case the analyses were performed on those individuals who made premature responses (N=899). All subject response data were recorded, however this sample is reduced as N=121 adolescents made no premature errors and therefore no information were available for them. The significant interaction in the rIFG is unaffected by this reduction in participants; $F(1,884)$ 4.96, $p<0.05$, eta²0.006, males with CD showed significantly greater rIFG response compared to females with CD ($p<0.05$), this effect is significant at Model 3. This analysis was also repeated for the reduced sample matched to those individuals for whom SST reaction time data were available (N=551); the significant interaction effect remained; $F(1,536)$ 6.46, $p<0.05$, eta²0.012; males with CD showed significantly greater rIFG response compared to females with CD ($p<0.05$), this effect was significant at model three and there were no additional significant effects.

Table 36 Post-Hoc Comparisons for each Model of the Gender-by-Group Interaction in the Right Inferior Frontal Gyrus Region of Interest Analysis

| **Post-Hoc Comparisons** | **Contrast** | ***p*** |
|---|---|---|
| Model 1 (Site, handedness) | CD Males > Control Males | 0.30 |
| | CD Males > CD Females | 0.014* |
| | CD Males > Control Females | 0.097 |
| Model 2 (Site, handedness, Verbal IQ) | CD Males > Control Males | 0.30 |
| | CD Males > CD Females | 0.014* |
| | CD Males > Control Females | 0.096 |
| Model 3 (Site, handedness, Verbal IQ, Hyperactivity/Inattention) | CD Males > Control Males | 0.55 |
| | CD Males > CD Females | 0.016* |
| | CD Males > Control Males | 0.28 |

*Bonferroni corrected for multiple comparison, $p<0.05$

## 5.5 **Discussion**

*This study explored the extent to which adolescents with CD problems show deficits in two domains of executive function; working memory and inhibitory control. Adolescents with CD problems showed impairments in spatial working memory compared to control adolescents, an effect that was independent of differences in IQ between the groups and of symptoms of ADHD. In terms of inhibitory control the CD adolescents made significantly more impulsive errors on the stop signal reaction time task compared to control adolescents, however when group differences in verbal IQ and symptoms of ADHD were both controlled for the between group differences diminished. At the neural level there was a significant Gender-by-Group interaction in the Inferior Frontal Gyrus; males with CD showed a significantly greater BOLD response compared to females with CD, while in controls there was no gender difference.*

***Main effect of Group: Neuropsychological Measures***

Consistent with previous reports (Syngelaki *et al.,*2009; Barnett *et al.,*2009; Cauffmann *et al.,*2005) this study found that adolescents with CD problems showed significantly greater working memory deficits compared to control adolescents and that males and females were equally affected. This deficit was specific to the CANTAB Spatial Working Memory task; CD adolescents made significantly more "between-search" errors (the participant returned to search a box they have already located a counter in) compared to controls even when group differences in IQ and symptoms of hyperactivity/inattention were controlled for. There was also a significant main effect of group on search strategy of the SWM task; the CD group performed less efficient searches compared to the control group although this effect diminished when verbal IQ was controlled for.

Good working memory ability is important for goal-directed behaviour; if one cannot accurately hold a goal in mind this could lead to inefficient strategies for goal execution. The findings from this study appear to suggest that this is characteristic of the CD group; they were less able to hold the location of a previously discovered counter in their working memory store and made inefficient search strategies to execute their goal; to find all of the counters. While the size of this effect was small, outside the experimental setting this finding could have practical implications. If a person has difficulty holding a goal in mind and formulating a strategy to allow that goal to be achieved then temporal relations between events and outcomes may never be formed. This could mean that a person's behaviour becomes driven more by stimuli in their immediate environment or by rewarded behaviour, rather than by well thought out planned actions.

Consistent with the findings of Herba *et al.,*(2006) this study found adolescents with CD problems showed deficits in motor inhibition; evidenced here by inhibition errors on the stop signal reaction time task. Earlier in this thesis (Chapter 3) it was reported that the CD group

also showed significantly greater average trait impulsivity compared to controls. This suggests that the CD group do show difficulties exercising self-control over their impulses which could explain why they may participate in behaviours that are detrimental. Taken together, the deficits in both domains may contribute more to the CD phenotype than initially thought. The study by Cauffman *et al.,*(2005) suggested that these two abilities are actually strongly linked; the researchers found that better spatial working memory was significantly associated with greater reported self-control.

***Gender-by-Group Interaction: Neural Reactivity***

It was predicted that neurofunctional reactivity in the right inferior frontal gyrus during the Stop Signal fMRI task would vary according to group; specifically that CD adolescents would show greater BOLD responses compared to controls, however no such effect was found. Previous literature had suggested that this prediction was valid; children and adolescents with CD have been shown to have difficulty with response inhibition (van der Meer & van der Meere, 2004; Schoemaker *et al.,*2012; Dougherty *et al.,*2003), so the assertion that this group would need to allocate more neural resources (evidenced by greater rIFG BOLD response) in order to perform as well as the control group was appropriate. While the CD group did make more premature responses compared to controls it appears that when they successfully inhibited their motor response, their neural response, at least in the rIFG, did not differ significantly from the control group. A recent review by Arnsten and Rubia (2012) postulated that dysfunctions in this area of the prefrontal cortex are more associated with ADHD symptoms, while children and adolescents with CD show deficits related to motivation and affect. Correcting for the effects of ADHD (hyperactivity/inattention symptoms) made no difference in this case; when the model did not correct for these symptoms there was still no overall main effect of CD. As this inhibition task did not contain a rewarding element this might explain the comparable performance of CD adolescents compared to the control group.

While rIFG responses did not vary overall according to group there was a significant Gender-by-Group interaction; males with CD showed significantly greater rIFG BOLD responses compared to females with CD, while reactivity did not vary according to gender in controls. This finding is interesting as it was not expected. Indeed, previous work had suggested that females with CD problems were as affected as males with CD problems in terms of response inhibition (Herba, Tranah, Rubia, & Yule, 2006). This interaction effect remained even when verbal IQ and symptoms of hyperactivity/inattention were controlled for. Two studies by Li and colleagues have investigated gender differences in the neural correlates of cognitive control in adults and found greater activation in males, compared to females, in a distributed set of regions including the middle and medial frontal cortices (Li *et al.,*2006; Li *et al.,*2009). Behaviourally they found no evidence for differences between males and females, as this study did not either; however they did find differences in regional brain activation during the stop phase. The authors asserted that males required more "neural resources" to achieve the same level of behaviour as females. This study did not precisely replicate these findings; one would have expected there to also be an overall main effect of gender, which there was not, gender differences were isolated to the CD group. Nevertheless this finding is novel and provides preliminary evidence to suggest that while males and females with CD perform similarly on behavioural measures of EF, at the neural level they are very different.

The findings reported in Chapter Three of this thesis did not indicate that CD males showed significantly greater average trait impulsivity compared to CD females, neither were there significant differences in the number of premature responses made on the stop signal task as a function of gender in the CD group. As the other measures of trait impulsivity investigated in this thesis showed no such interaction effects it is possible that this finding could be a consequence of cortical immaturity in CD Males compared to CD Females. As the brain

matures across development cortical gray matter volumes decrease as a function of synaptic pruning and myelination (Giedd, 2004). It is proposed that gray matter thickness is related to cognitive ability (Casey, Tottenham, Liston, & Durston, 2005), a proposition supported by a recent investigation by Kharitonova and colleagues (2013). The authors found that performance on a cognitive control task was associated with thinning of the right inferior frontal gyrus (Kharitonova, Martin, Gabrieli, & Sheridan, 2013). It is possible that the difference in neural reactivity between CD males and females in this task may have been a consequence of less efficient neural responses to inhibition manifesting as larger BOLD responses as a result of less mature cortical regions. The dorsal lateral prefrontal cortex is one of the last areas to mature and does not reach adult dimensions until at least 20 years old (Giedd, 2004). One potentially interesting future study would be to explore cortical development in the prefrontal cortex through volumetric analysis of cortical gray matter thickness, exploring the extent to which males and females with and without CD may show differential volumes.

***Verbal IQ and Hyperactivity/Inattention Symptoms***

One of the aims of this study was to investigate the effect of controlling for between-group differences in verbal IQ and also symptoms of ADHD. Previous research, with some notable exceptions (Hobson *et al.,*2011), has neglected to assess fully the contributions of both of these factors, which can have important influences on executive function performance. This study attempted to overcome this limitation by exploring between-group differences using three statistical models. Symptoms of hyperactivity/inattention were used to account for behaviours related to ADHD and were controlled for in this study. This was due to a number of individuals scoring in the abnormal range. While these scores were not high enough to result in a separate group of individuals (CD+ADHD) they could have been high enough to contribute to variation in executive function performance.

IQ is related to executive function ability, so not adequately controlling for between-group differences in IQ can make a difference to the magnitude of effects reported. This study reported a significantly greater average verbal IQ score in the control group compared to controls. This finding reiterates the importance of exploring the extent to which executive function deficits observed in clinical groups could not be otherwise attributed to known group differences in intelligence when examining performance between-groups. Had the relative contributions of both verbal IQ and hyperactivity/inattention symptoms not been explored then this study might have come to the incorrect conclusion that impulsive premature responses on the SSRT and a poor use of strategy during the spatial working memory task were also core features characteristic of males and females with CD problems. One possible disadvantage of controlling for IQ differences could be that lower IQ is in fact a core component of the CD phenotype and adjusting for these effects could remove variance associated with the disorder itself. Such a proposition would require more sophisticated analyses than have been presented here, however this would represent an interesting further investigation.

***Conclusion***

Consistent with previous reports this study provides evidence that CD problems are associated with executive function problems in both inhibitory control and working memory. It is possible that deficits in working memory ability may mean the CD adolescents are unable to form clear goals due to a reduced capacity to formulate and follow coherent strategies. This study also provided new evidence that CD males and females show differences in neural reactivity during a response inhibition task. Males with CD showed significantly greater inferior frontal gyrus activation during response inhibition compared to CD females which might reflect greater effort to achieve comparable performance or differences in cortical maturity.

# Chapter 6 Risk Taking and Reward Processing

*This study investigated the extent to which adolescents with conduct disorder problems showed difficulties with measures of hot executive function ability using a neuropsychological gambling task and explored the neural mechanisms of reward sensitivity using a Monetary Incentive Delay fMRI paradigm. The extent to which hot executive function deficits prevail in conduct disorder and the extent to which these difficulties differed in males and females and as a function of callous-unemotional traits were also explored.*

## 6.1 Introduction

Our health and wellbeing are largely determined by the outcomes of choices we make. We feel happy when an outcome is positive or exceeds our expectations and feel frustration or disappointment when an outcome is negative, or less than we feel we deserve. Reward related decision making is the combination of internally monitoring behaviour and evaluating the value of external stimuli that motivates our actions, and may be important for monitoring the appropriateness of behaviour. It is therefore extremely important for healthy development.

There is a growing body of evidence suggesting that disruptions in "Hot" EFs such as reward related decision making, may contribute to the aetiology of Conduct Disorder (CD) problems. Disruption in these processes, particularly during adolescence, may make this group vulnerable to heightened risk taking and experimentation with substances such as alcohol and drugs. Indeed CD is associated with a risk for developing substance use problems by late adolescence (18 years old; Elkins *et al.,*2007) and early adulthood (26 years old; Moffitt *et al.,*2002). This emphasises the importance of studying this group at an earlier age to identify behavioural or

neurobiological markers that may predispose the group to risk taking or aberrant reward processing.

### *Theoretical Underpinnings of Risk Taking and Reward Dysfunction*

Self-regulation is the 'effortful monitoring, evaluating, and, if need be, altering of behaviour' (Newman & Wallace, 1993). In their review Newman and Wallace propose that self-regulation requires the integration of a variety of motivational (e.g. affective or rewarding) and cognitive factors (e.g. attentional/cool executive functions). One of the most prominent theories of self-regulation is Gray's reinforcement sensitivity theory (Gray, 1987). Gray proposed three arousal systems; the Behavioural Activation System (BAS), Behavioural Inhibition System (BIS) and the Nonspecific Activation System (NAS). The BAS is proposed to be sensitive to reward, while the BIS is sensitive to punishment and both compete to increase NAS activity to override activity in the other system. A similar hypothesis has been proposed by Ernst and colleagues (2006) who pinpointed these behaviours to specific neural structures. The authors proposed that risk taking and reward seeking (goal directed) behaviours are a consequence of the aberrant function of three important neural structures; the amygdala, nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC). Particularly, the authors suggested an overactive reward system (NAcc) coupled with a weak harm-avoidance system (amygdala) and inefficient higher order cognitive control system (mPFC) could give rise to abnormal levels of reward oriented behaviours (Ernst, Pine, & Hardin, 2006). It is therefore possible that conduct disorder problems could arise as a consequence of an overactive BAS/Reward system and faulty BIS system. Evidence from behavioural and neuroimaging investigations supporting these theories are reviewed in the following sections.

***Behavioural and Neuropsychological Evidence for "Hot" Executive Dysfunction in Conduct Disorder***

Neuropsychological studies have suggested that decision making, particularly during rewarding conditions, is altered in youths with CD problems. Individuals with CD/antisocial behaviour problems appear to make decisions based on rewards they have received rather than on how risky that choice might be, waging larger sums on gambling tasks following the receipt of small rewards (Fairchild *et al.,*2009; Syngelaki *et al.,*2009) and showing a preference for large rewards despite increasing penalties (Luman *et al.,*2010). There is also some evidence to suggest that youths with CD/Oppositional Defiant problems are less sensitive to punishment than their peers (Matthys *et al.,*2004), a finding that is also common to individuals with CU/Psychopathic traits.

Evidence for disturbances in sensitivity to punishment come mainly from passive-avoidance tasks. These tasks tap reversal-learning and test how well the individual is able to adjust their responses when a stimulus set changes contingency. One of the most consistent findings is that individuals with high CU or psychopathic traits are unable to switch their responses when contingencies change, specifically when a previously rewarded stimulus becomes punished (Newman & Kosson, 1986). O'Brien & Frick (1996) investigated reward processing in a clinical sample of children and adolescents and found that while CD problems were related to a reward-dominant style (continuing with trials despite a loss of points), high CU traits were also associated with reward-dominance, regardless of the presence of CD problems. More recent evidence supporting the independent contribution of CU to a reward oriented style comes from Centifanti and Modecki (2013) who investigated reward and punishment sensitivity in a community adolescent sample of males and females when they were in groups and when they were alone. They found that when the adolescents were alone, those with high CU were less sensitive to accruing rewards, and that females demonstrated a stronger reaction to

punishment compared to males. In the group condition the authors found males with High CU showed greater risk taking behaviour compared to males with Low CU traits. The authors suggested that this was as a consequence of the High CU male asserting his authority, or dominance, over the experimental situation. Conversely they found that High CU females were slower to take risks and were slower to respond following punishment compared to Low CU females. The authors suggested that this difference may be a reflection of the difference in harm processing between males and females.

### *Neural Basis of Reward Processing*

A number of brain regions are involved in reward related decision making. A recent meta-analysis by Liu and colleagues (2011) reviewed neuroimaging studies that examined brain activation in reward related tasks. They found distinct patterns of activation in a number of regions and also investigated different phases of reward processing. The anticipation of reward activated regions including the ventral striatum, anterior insula, medial orbitofrontal cortex, anterior cingulate cortex, inferior parietal lobule and dorsolateral prefrontal cortex. Reward feedback activated the ventral striatum, anterior insula, medial orbitofrontal cortex, amygdala, anterior cingulate cortex and dorsolateral prefrontal cortex.

### *fMRI Evidence for "Hot" Executive Dysfunction*

There is evidence to suggest that differences in reward and punishment processing may be associated with aberrant neural responses in CD youths with and without CU/Psychopathic traits. Research has examined different phases of reward processing (anticipation and outcome) under differing rewarding or punishing contingencies, although the findings of these studies are quite mixed. Some fMRI studies have found no differences in neural reactivity during the anticipation of reward in youths with CD compared to control participants (Bjork *et*

*al.,*2010). However mixed findings have been found during reward notification; one study found that CD youths show greater neural reactivity in response to the receipt of reward (Bjork *et al.,*2010) however another study did not (Gatzke-Kopp *et al.,*2009). There is also evidence to suggest that individuals with psychopathic personality traits also show differences in reinforcement signalling at the neural level.

Buckholtz and colleagues (2010) found in a community recruited sample of volunteers that impulsive antisocial personality traits were associated with increases in nucleus accumbens response during the anticipation of reward. A more recent study by Bjork and colleagues (2012) replicated this effect, also finding that in a community sample trait psychopathy was associated with increased neural response in the ventral striatum and anterior cingulate cortex during reward anticipation. Finger and colleagues (2011) found that youths with CD/ODD and high psychopathic traits showed disruption (less reactivity compared to controls) in areas important for value representation and reward processing (orbitofrontal cortex and caudate) during a reversal learning task.

Overall the evidence for hypo-or hypersensitivity to reward outcome in individuals with CD is mixed and could be due, at least in part, to the heterogeneous presentation of CD symptoms and also to the distinction that perhaps should be made on the basis of the presence or absence of callous-unemotional traits (see Table 37 and Table 38 for a summary).

***Gender Differences in Risk Taking and Reward Processing***

There is evidence to suggest that males and females may differ in risk taking behaviour and also show different reward sensitivity. Two investigations have found evidence to suggest that males show more novelty seeking behaviour; behaviour associated with novel situations and

also lower harm avoidance compared to females (Cloninger, Przybeck, & Svrakic, 1991; Romer & Hennessy, 2007). In their longitudinal investigation, Romer and Hennessy (2007) found that females showed lower sensation seeking (a drive to seek out novel and exciting experiences) compared to males. The authors found greater risk taking measured by higher drinking, tobacco smoking and cannabis smoking behaviour among males compared to females, and that males perceived these activities as less risky. An investigation into reward and punishment sensitivity by Li and colleagues also found that males showed greater trait reward sensitivity compared to females, however the groups did not differ on a measure of punishment sensitivity (Li, Huang, Lin, & Sun, 2007).

In addition to behavioural and trait indices suggesting gender differences in risk taking and reward sensitivity there is evidence to suggest that males and females may differ in neural reponse. Spreckelmeyer and colleagues (2009) used a modified version of a monetary incentive delay task to investigate whether socially rewarding stimuli (smiling face) elicited similar patterns of neural response to those activated by the anticipation of monetary reward, and investigated whether these patterns of response varied according to gender. The authors found that females showed stronger activation in the caudate in response to increasing socially rewarding stimuli compared to males while males showed stronger activation to increasing anticipated monetary reward compared to women in the putamen.

These differences have important implications for this chapter, where variations in risk taking and reward sensitivity as a function of gender are investigated.

Table 37 Summary of Behavioural Findings: Risk Taking and Reward Processing in Conduct Disorder Problems ± Callous Unemotional Traits

| Authors | Task | Age Group | Sample | Gender | Impairment |
|---|---|---|---|---|---|
| Fairchild, van Goozen, Stollery, Aitken, Savage, Moore & Goodyer (2009) | RCT | 14-18 | Clinical<br>E-O CD (n38)<br>A-O CD (n34)<br>Control (n84) | Male | Increased motivation led to more cautious decisions in all groups<br>E-O/A-O > Control: Made more risky choices<br>E-O > A-O & Control: Selected risky choice after small gain |
| Centifanti & Modecki (2013) | BART Task | 16-20 | Community (n675)<br>CU Traits | M & F | High CU Males make quicker decisions to take risks vs. Low CU Males in a group setting.<br>CU Youths overall less sensitive to accruing rewards<br>High CU Females slower to take risks and slower to respond after punishment vs. Low CU Females |
| Hobson, Scott & Rubia (2011) | IGT | 10-17 | Clinical<br>CD/ODD (n28)<br>ADHD±CD/ODD (n31)<br>Controls (n34) | M & F | Number of Risky Decisions<br>CD/ODD > Control<br>ADHD > Control |
| Dougherty, Bjork, Harper, Marsh, Moeller, Mathias & Swann (2003) | Reward Directed Impulsivity Paradigm | 13-17 | Clinical<br>DBD (n22)<br>Control (n22) | M & F | CD/ODD twice as many reward directed responses compared to controls. |
| Syngelaki, Moore, Savage, Fairchild & Van Goozen (2009) | RCT | 12-18 | Offenders (n102)<br>Controls (n83) | Male | Offenders gambled more than controls<br>Offenders chose more risky option than controls<br>Offenders gambled even after a small win, |

| Authors | Task | Age Group | Sample | Gender | Impairment |
|---|---|---|---|---|---|
| | | | | | controls did not |
| Luman, Sergeant, Knol & Oosterlaan (2010) | Gambling Task with different reward contingencies | 7-12 | Clinical<br>ODD (n18)<br>Control (n24) | M & F | ODD greater preference for larger rewards compared to controls |
| Matthys, van Goozen, Snoek, van Engeland (2004) | Passive-Avoidance Learning Task | 7-12 | Clinical<br>CD/ODD (n19)<br>Control (n20) | Male | CD/ODD less sensitive to punishment shown by response perseveration to a punishing stimulus |
| O'Brien & Frick (1996) | Passive-Avoidance Learning Task | 6-13 | Clinical<br>CD (n92)<br>Control (n40) | M & F | CD related to a reward-dominant style - played more trials despite loss of points<br>High CU associated with a reward-dominant style regardless of conduct problems. |

BART: Balloon Analogue Risk Taking Task; RCT: Risky Choice Task; WCST: Wisconsin Card Sorting Task; CU: Callous-Unemotional Traits; IGT: Iowa Gambling Task; DBD: Disruptive Behaviour Disorder (Conduct Disorder (CD)/Oppositional Defiant Disorder (ODD)/Attention-Deficit/Hyperactivity Disorder (ADHD)

Table 38 Summary of fMRI Findings: Risk Taking and Reward Processing in Conduct Disorder Problems ± Callous Unemotional Traits

| Authors | Task | Age Group | Sample | Gender | Impairment |
|---|---|---|---|---|---|
| Bjork, Chen, Smith & Hommer (2010) | MID | 13-17 | Clinical AED (n12)<br>Controls (n12) | M & F | Condition: Notification of Reward vs. Notification of Failure. AED > Control NAcc |
| Finger, Marsh, Blair, Reid, Sims, Ng, Pine & Blair (2011) | Passive Avoidance | 12-16 | Clinical CD/ODD + High Psychopathy (n15)<br>Controls (n15) | M & F | CD/ODD+Psychopathy reduced OFC and caudate to stimulus-reinforcements.<br>CD/ODD+Psychopathy reduced OFC to rewards |
| Gatzke-Kopp, Beauchaine, Shannon, Chipman, Fleming, Crowell, Liang, Johnson & Aylward (2009) | MID | 12-15 | Clinical CD/ADHD (n19)<br>Control (n11) | Male | Condition: Non-reward vs. Reward<br>Controls > CD/ADHD in the ACC |
| Bjork, Chen & Hommer (2012) | MID | 22-43 | Community (n31) | M & F | Psychopathy associated with increased VS and ACC response during reward anticipation |

MID: Monetary Incentive Delay Task; AED: Adolescents with Externalising Disorders; NAcc: Nucleus Accumbens; OFC: Orbitofrontal Cortex; VS: Ventral Striatum; ACC: Anterior Cingulate Cortex

This thesis used an fMRI paradigm designed by Knutson and colleagues (2000), the Monetary Incentive Delay (MID) to investigate different phases of reward processing. This task is particularly suitable as it allows the exploration of reward related activation patterns at different positively and negatively valenced stages of reward. This thesis examines three stages; (i) the anticipation of a positive reward, (ii) feedback that a positive reward had been won and (iii) feedback that a positive reward had not been won (reward omission).

***Regions of interest***

Different regions were a priori selected for analysis dependent on the reward condition. For the first stage, the anticipation of a positive reward, three regions of interest were selected; the ventral striatum, amygdala and medial orbitofrontal cortex. These regions were selected as all had previously been implicated as important for reward related processing (e.g. Liu and colleagues, 2011) or aberrant in youths with CD problems. The ventral striatum responds during the anticipation of reward (Knutson *et al.,*2000) and has been suggested to play a role in the representation of reward amounts (Diekhof, Kaps, Falkai, & Gruber, 2012), which is suggestive of a role in reward-related learning. Researchers have also suggested that ventral striatal activity is at its greatest when participants expect to be rewarded for their decision with high certainty (Heekeren *et al.,*2007). Therefore one would predict significant activation in the ventral striatum on the basis that this contrast models the maximally rewarding condition. The amygdala is important for anticipation of reward because it projects to the ventral striatum (Haber & Knutson, 2010). It has been previously shown to respond during the anticipation of monetary reward (Hommer *et al.,*2003) and also has been shown to function aberrantly in youths with CD problems and individuals with high CU traits. The medial orbitofrontal cortex was selected as it is has been shown to respond to monetary rewards (Thut *et al.,*1997). Therefore as all three areas; ventral striatum, amygdala and medial orbitofrontal cortex have been shown to be moderated by reward sensitivity, and due to their

reported connectivity (Costumero *et al.,*2013), all three were selected for analysis in this contrast.

This study investigated two feedback phases of reward processing. During the notification of reward receipt (positive outcome) three regions of interest were selected; the amygdala, anterior cingulate and medial orbitofrontal cortex. The amygdala is important for processing positive reward feedback because it is involved in stimulus-reinforcement learning (Everitt *et al.,*2003), so aberrant function in the amygdala during positive reward notification may be indicative of a reduced ability to process rewards and from there to form sensible, typical, associations between stimuli. The anterior cingulate cortex is a good candidate to investigate neural processes during reward notification as it has been implicated in reward related decision making (Bush *et al.,*2002), probabilistic reward learning (Santesso *et al.,*2008) and has been shown to respond during the notification of positive rewards like winning (Rogers *et al.,*2004). The medial orbitofrontal cortex has been shown to respond preferentially to the notification of positive reward (Rogers *et al.,*2004) and may process the magnitude of the received reward (Diekhof *et al.,*2012). All three regions had been found to be significantly activated during reward feedback by Liu and colleagues (2011) and have been suggested to show aberrant function in youths with conduct/oppositional problems and high CU traits (Finger *et al.,*2011).

The second feedback phase was the notification of reward miss (negative outcome). Two regions of interest were selected; the insula and anterior cingulate cortex. The insula has been shown to respond to the notification of losses in adolescents with and without symptoms of externalising difficulties (Bjork *et al.,*2010) and also during a punishment phase of a risky decision making task (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003). As such, although this contrast did not explicitly index punishment, the insula was included as a region of interest

due to its role in processing aversive conditions (Paulus *et al.,*2003; Paulus and Stein, 2006). The anterior cingulate cortex was selected as the other region of interest for this contrast as it has been suggested to have a role in risk assessment (Rogers *et al.,*2004) and responds to both reward and punishment (Simoes-Franklin, Hester, Shpaner, Foxe, & Garavan, 2010). As this particular contrast examines the omission of an expected reward and is the most representative of punishment it was included in this study.

***Hypothesis and Predictions***

This study is concerned with investigating hot executive processes of risky decision making and incentive processing that have been previously been implicated as dysfunctional in individuals with CD problems with and without CU traits.

It was predicted that the adolescents with CD would show a greater propensity for risk taking by making greater wagers overall, and in circumstances where the odds seemed more in their favour compared to the control adolescents. It was expected that this effect would vary according to gender, and that males would show greater risk taking compared to females. The extent to which these gender differences persisted also within the CD group were investigated. It was also predicted that risk taking would vary according to CU traits, and High CU traits would be associated with a greater overall propensity for risk taking and would exacerbate (increase) risk taking in the CD group.

In terms of neural reactivity it was expected that, consistent with previous reports (Bjork *et al*, 2010), adolescents with CD would not show significant differences in neural reactivity during the anticipation of reward. It was expected that High CU would be associated with a reward-dominant style and therefore would be associated with increased reactivity in the ventral

striatum during reward anticipation. The extent to which these effects were moderated by gender were explored; previous research suggested that males would show greater activity during the anticipation of reward compared to females (Spreckelmeyer *et al.,*2009). The extent to which High CU moderated the reactivity in the CD adolescents was also explored.

It was predicted that the notification of a large reward would be associated with increased responses of all three regions of interest in adolescents with CD compared to controls and the extent to which this varied according to gender was explored. It was additionally predicted that High CU would be associated with increased BOLD responses in all three regions and that CU would moderate the effect of CD, resulting in comparably greater activation in the CD plus High CU group compared to the CD group with Average CU.

Finally, it was predicted that the notification of no reward would be associated with significantly lower BOLD response in both regions of interest in the CD adolescents compared to the control adolescents and that this effect would be exacerbated by the presence of High CU traits in the CD youths. As this contrast is the most similar to punishment available in the study, and that previous research suggested that males and females did not vary according to their punishment sensitivity (Li *et al.,*2007) overall it was not expected that there would be a main effect of gender on reactivity. However as Centifanti and Modecki (2013) recently found evidence to suggest that males and females may differ in their responses to punishment when they have High CU, possible interaction effects were explored.

## 6.2 **Method**

***Participants***

Participants with Conduct Disorder Problems (CD) were those classed as 'possible' or 'probable' CD cases (N=172) according to the Strengths and Difficulties Questionnaire (SDQ). All participants classed as 'unlikely' to develop CD are referred to as Controls (N=864). Adolescents with 'High CU' were those who scored more than one standard deviation above the mean (a score of 7 or more; N=174), the 'Average CU' group were those who scored between 0-6 points (N=862), see Chapter Two, section 2.2 for further information.

Group characteristics (mean, standard deviation) for demographic variables may be found in Table 39 and Table 40 and test statistics in Appendix Chapter 6, Table 74 and Table 75. There was a significant main effect of gender on Verbal IQ score; males had a significantly higher Verbal IQ compared to females ($F(1,1022)$ 5.06, $p<0.05$. eta²0.05). There was also a significant main effect of gender on symptoms of Hyperactivity/Inattention; males had a significantly greater symptom count score compared to females ($F(1,1022)$ 17.65, $p<0.001$, eta²0.02). There was a significant main effect of group on symptoms of Hyperactivity/Inattention; the CD group had a significantly greater symptom count score compared to the controls ($F(1,1022)$ 96.36, $p<0.001$, eta²0.08). Participants with complete data that passed fMRI task specific outlier criteria in terms of movement, spike detection, were able to view the task stimuli without obstruction and did not show anatomical abnormalities were included in the analysis. Individuals with good neuropsychological data were also included. In total N=1036 individuals had full datasets for the three MID task contrasts and CANTAB Gambling Task measures.

Table 39 Descriptive Statistics: Demographic Variables for Chapter Six [Males Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=41)** | **Average CU (N=55)** | **High CU (N=83)** | **Average CU (N=309)** |
| Age | 14.45 (0.42) | 14.38 (0.40) | 14.34 (0.41) | 14.39 (0.39) |
| Verbal IQ | 114.63 (15.83) | 109.73 (17.91) | 114.18 (17.75) | 114.46 (14.30) |
| Performance IQ | 106.20 (18.80) | 107.31 (16.82) | 108.63 (14.51) | 110.12 (13.04) |
| Hyperactivity/Inattention | 5.24 (2.77) | 4.91 (2.48) | 3.41 (2.12) | 2.67 (1.92) |

Table 40 Descriptive Statistics: Demographic Variables for Chapter Six [Females Mean (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| **Measure** | **High CU (N=19)** | **Average CU (N=57)** | **High CU (N=31)** | **Average CU (N=441)** |
| Age | 14.39 (0.38) | 14.42 (0.44) | 14.39 (0.42) | 14.42 (0.41) |
| Verbal IQ | 110.89 (20.35) | 106.23 (15.49) | 110.94 (16.08) | 110.22 (14.32) |
| Performance IQ | 109.84 (16.26) | 102.74 (13.94) | 108.54 (15.18) | 109.09 (13.81) |
| Hyperactivity/Inattention | 3.89 (1.82) | 4.47 (2.43) | 2.26 (2.13) | 2.08 (1.86) |

***Materials and Methods***

*Standardised Assessment Tools*

Risk taking was measured using the CANTAB (for task details please see Chapter Two, section 2.2). Two dependent variables were used; Overall Proportion Bet and Risk Taking. Overall Proportion Bet indexed the average proportion of the current point total that the participant was willing to risk on each gamble trial. A larger proportion indicated the person was more risk taking. The risk taking variable was calculated as the mean proportion of the current points total that the subject was willing to risk on a trial when they had chosen the more likely outcome, and so measured how willing they were to take risks when the 'odds' appeared more in their favour. The CANTAB was administered as part of the Institute visit.

***fMRI Paradigm***

Participants completed the MID task as described in Chapter Two section 2.3. The task was administered as part of a larger battery during the second of two imaging acquisition sessions; see Chapter Two Section 2.3.

***fMRI Data Acquisition and Analysis***

Structural and functional MRI data were acquired at eight IMAGEN assessment centres with 3T MRI scanners of different manufacturers, as described in Chapter Two section 2.3. In the second level random effects analysis one sample t-tests were used to identify brain regions that showed significant activation during (i) Anticipation Large Win vs. Anticipation No Win, (ii) Feedback Success Large Win vs. Feedback No Win, (iii) Feedback Missed Large Win vs. Feedback No Win. Summary statistical maps were thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for gender, site and handedness.

*Region of Interest (ROI) Analyses*

ROIs were extracted dependent on the contrast under investigation. For the "Anticipation Large Win vs. Anticipation No Win" contrast three regions were selected; ventral striatum (VS), amygdala (AMYG) and medial orbitofrontal cortex (mOFC). The VS ROI was extracted based on the peak from the random effects analysis of this contrast (xyz ±9 11 -2, 9mm sphere), the AMYG and mOFC ROIs were extracted based on the Montreal Neurological Institute (MNI) Automated Anatomical (AAL) ROI database. For the "Feedback Success Large Win vs. Feedback No Win" contrast three regions were selected; anterior cingulate cortex (ACC), amygdala (AMYG) and medial orbitofrontal cortex (mOFC). All were extracted based on the MNI AAL ROI database. For the "Feedback Missed Large Win vs. Feedback No Win" contrast two regions were selected; the anterior cingulate cortex (ACC) and insula (INS), both were extracted based

on the MNI AAL ROI database. The beta values for responses during each contrast were extracted using the MARSBAR toolbox (http://marsbar.sourceforge.net) and the data exported for group-level analyses in SPSS.

*Statistical Analysis*

All analyses in this chapter were performed using SPSS V.20. Analyses of covariance (ANCOVA) were conducted using the General Linear Model. Independent factors included CD Group (Case vs. Control), Gender and CU (High vs. Average). Interactions between the factors were explored and two- and three-way interactions were modelled. The main effects were centralised to avoid multicollinearity between the main effect and interaction terms within the model. The full model was modelled first in each instance including all main effects, 2-way interactions and the 3-way interaction. Where the 3-way interaction was not significant the term was removed from the model so that the 2-way interactions could be better investigated. To account for any local differences in recruitment strategy assessment site was controlled for in all analyses. For the region of interest analysis handedness (left/right/ambidextrous) was added additionally controlled for.

## 6.3 **Results: Cambridge Gambling Task**

See Table 42 for descriptive statistics and Appendix Chapter 6, Table 76 for test statistics. See Table 41 for a summary of significant effects.

Table 41 Summary of Significant Main and Interaction Effects Cambridge Gambling Task

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| Overall Proportion Bet | × | × | × | × |
| Risk Taking | × | × | × | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| Overall Proportion Bet | × | × | ✓ | |
| Risk Taking | × | × | ✓ | |

***Main effect of Gender***

There was a significant main effect of gender for both variables; in each instance males wagered proportionally larger sums compared to females. There were no other significant main effects or interactions.

Table 42 Descriptive Statistics Cambridge Gambling Task Measures: Mean (SD)

| | **Males** | | **Females** | |
|---|---|---|---|---|
| | **CD (N=96)** | **Control (N=392)** | **CD (N=76)** | **Control (N=472)** |
| **Overall Proportion Bet** | 0.52 (0.13) | 0.52 (0.13) | 0.47 (0.13) | 0.46 (0.14) |
| **Risk Taking** | 0.58 (0.13) | 0.57 (0.13) | 0.51 (0.14) | 0.50 (0.15) |

## 6.4 **Results: fMRI Paradigm: Reward Sensitivity**

***MID Task: Anticipation Large Win vs. Anticipation No Win Random Effects Analysis***

A one sample t-test was performed to identify brain regions significantly activated in the Anticipation Large Win vs. Anticipation No Win contrast. The summary statistical map was thresholded at $p<0.05$ (FWE; Family-Wise Error Corrected) and controlled for the effects of handedness, site and gender. Significant activation was found across the brain, the cluster was very large (k>25,000 voxels) and included subcortical areas such as the caudate, nucleus accumbens, thalamus and putamen, and cortical regions such as the cingulate gyrus, insula and medial frontal areas. Additional significant clusters included occipital visual areas, see Figure 24 and Table 43.

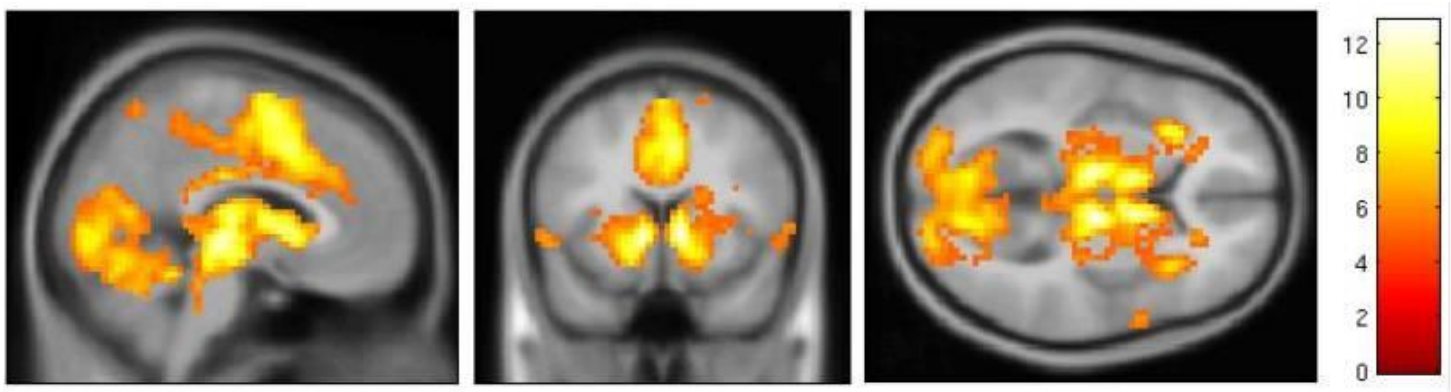


Figure 24 Random Effects Clusters for the MID Task 'Anticipation Large Win vs. Anticipation No Win' Contrast (Full Sample)

Table 43 Significant Random Effects Clusters for the MID Task 'Anticipation Large Win vs. Anticipation No Win' Contrast (Full Sample)

| **Full Sample Random effects analysis** | | | | | **Cluster** |
|---|---|---|---|---|---|
| **Brain Region of Activation (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Caudate, Nucleus Accumbens, Posterior Cingulate Gyrus | 29 | 9 11 1 | 25854 | Inf | <.0001 |
| Temporal Pole | | 27 38 -29 | 33 | 5.39 | .042 |
| Temporal Pole | | -33 23 -38 | 55 | 4.87 | .003 |

***MID Task: Anticipation Large Win vs. Anticipation No Win Region of Interest Analysis***

Three regions of interest were analysed; the ventral striatum, amygdala and mOFC. As no specific prediction was made regarding which hemisphere or which region was most relevant, a Bonferroni correction for multiple comparison was applied and the threshold for significance adjusted to $p<0.008$. Test statistics for each ROI can be located in Appendix Chapter 6, Table 77 - Table 79. A summary of significant main and interaction effects for this contrast may be found on Table 46.

Table 44 Descriptive Statistics for the MID Task 'Anticipation Large Win vs. Anticipation No Win' Contrast Regions of Interest [Males Mean Beta Values (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| | **High CU (N=41)** | **Average CU (N=55)** | **High CU (N=83)** | **Average CU (N=309)** |
| **l AMYG** | 0.21 (0.50) | 0.13 (0.42) | 0.24 (0.57) | 0.21 (0.52) |
| **r AMYG** | 0.22 (0.43) | 0.13 (0.45) | 0.24 (0.50) | 0.22 (0.43) |
| **l VS** | 0.67 (0.55) | 0.53 (0.45) | 0.72 (0.45) | 0.60 (0.49) |
| **r VS** | 0.75 (0.60) | 0.56 (0.58) | 0.86 (0.54) | 0.67 (0.56) |
| **l mOFC** | -0.01 (0.63) | 0.01 (0.56) | 0.09 (0.57) | 0.09 (0.56) |
| **r mOFC** | 0.09 (0.40) | 0.07 (0.42) | 0.18 (0.44) | 0.14 (0.44) |

Table 45 Descriptive Statistics for the MID Task 'Anticipation Large Win vs. Anticipation No Win' Contrast Regions of Interest [Females Mean Beta Values (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| | **High CU (N=19)** | **Average CU (N=57)** | **High CU (N=31)** | **Average CU (N=441)** |
| **l AMYG** | 0.06 (0.81) | 0.02 (0.61) | 0.16 (0.45) | 0.20 (0.51) |
| **r AMYG** | 0.12 (0.49) | 0.13 (0.43) | 0.17 (0.45) | 0.18 (0.44) |
| **l VS** | 0.54 (0.35) | 0.65 (0.43) | 0.54 (0.45) | 0.60 (0.51) |
| **r VS** | 0.76 (0.47) | 0.73 (0.54) | 0.66 (0.47) | 0.69 (0.57) |
| **l mOFC** | -0.03 (0.55) | 0.02 (0.50) | 0.10 (0.47) | -0.03 (0.54) |
| **r mOFC** | 0.12 (0.40) | 0.09 (0.37) | 0.14 (0.42) | 0.05 (0.42) |

Table 46 Summary of Significant Main and Interaction Effects Region of Interest Analyses Anticipation Large Win vs. Anticipation No Win (MID Task)

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| L VS | × | × | × | ✓ |
| R VS | × | × | × | × |
| L AMYG | × | × | × | × |
| R AMYG | × | × | × | × |
| L mOFC | × | × | × | × |
| R mOFC | × | × | × | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| L VS | × | × | × | |
| R VS | × | × | × | |
| L AMYG | × | × | × | |
| R AMYG | × | × | × | |
| L mOFC | × | × | × | |
| R mOFC | × | × | × | |

***Gender-by-CU Interaction***

There was a nominally significant Gender-by-CU interaction in the left ventral striatum ($F$(1,1022) 4.92 p=0.027), although this effect did not survive correction for multiple region of interest analysis ($p$>0.008). Males with High CU showed significantly greater BOLD responses in the left ventral striatum compared to Males with Average CU ($p$<0.05). There were no effects in females, see Appendix Chapter 6, Figure 28.

***MID Task Feedback Success Large Win vs. Feedback No Win Random Effects Analysis***

A one sample t-test was performed to identify brain regions significantly activated in the Feedback Success Large Win vs. Feedback No Win contrast. The summary statistical map was thresholded at $p$<0.05 (FWE; Family-Wise Error Corrected) and controlled for the effects of handedness, site and gender. Significant activation clusters were found in the anterior and posterior cingulate cortex, paracingulate gyrus, inferior temporal gyrus, middle frontal gyrus, parahippocampal gyrus and occipital regions see Figure 25 and Table 47.

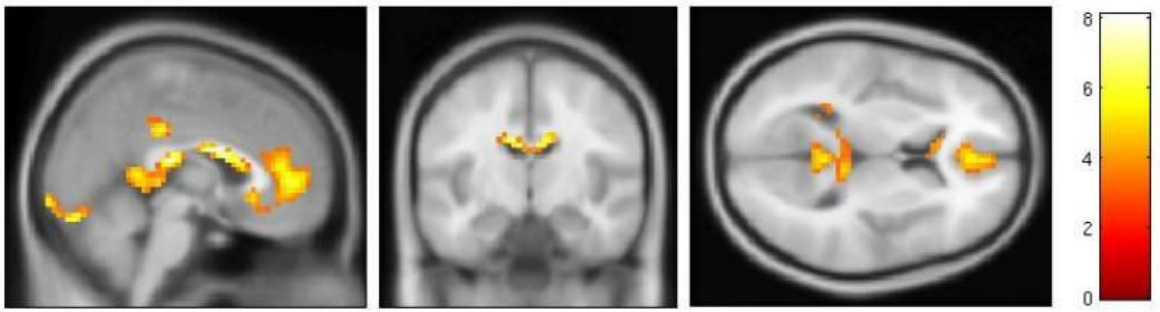


Figure 25 Random Effects Clusters for the MID Task 'Feedback Success Large Win vs. Feedback No Win' Contrast (Full Sample)

Table 47 Significant Random Effects Analysis Clusters for the MID Task 'Feedback Success Large Win vs. Feedback No Win' Contrast (Full Sample)

| **Full Sample Random effects analysis** | | | | | **Cluster** |
|---|---|---|---|---|---|
| **Brain Region of Activation (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Corpus Callosum | | 3 2 22 | 210 | Inf | $9.02^{-9}$ |
| Cerebellum, Precuneus | | 3 -25 16 | 343 | 7.75 | $1.97^{-12}$ |
| Occipital Cortex, Supramarginal Gyrus | 19 | 36 -67 49 | 461 | 7.42 | $2.66^{-15}$ |
| Lingual Gyrus, Occipital Pole | | 0 -85 -20 | 69 | 6.98 | 0.001 |
| Parahippocampal Gyrus | | -15 -25 -14 | 37 | 6.23 | 0.027 |
| Subcallosal Cortex, Anterior Cingulate Gyrus, Paracingulate Gyrus | 32 | 0 20 -8 | 303 | 6.07 | $2.16^{-11}$ |
| Occipital Cortex | 19 | -30 -70 46 | 126 | 5.77 | $4.86^{-6}$ |
| Posterior Cingulate Gyrus | 31 | 3 -34 34 | 37 | 5.57 | 0.027 |
| Supramarginal Gyrus | | -45 -49 46 | 46 | 5.4 | 0.009 |
| Inferior Temporal Gyrus | 20 | 57 -46 -11 | 97 | 5.36 | $5.8^{-5}$ |
| Occipital Cortex | | 48 -73 -23 | 37 | 5.26 | 0.027 |
| Parahippocampal Gyrus, Parahippocampal Gyrus | | 18 -25 -14 | 39 | 5.12 | 0.022 |
| Middle Frontal Gyrus, Superior Frontal Gyrus | 6 | 33 20 55 | 97 | 5.01 | $5.8^{-5}$ |
| Frontal Pole, Middle Frontal Gyrus | | 48 41 19 | 50 | 4.89 | 0.006 |
| Inferior Temporal Gyrus | 37 | -51 -58 -14 | 115 | 4.87 | $1.21^{-5}$ |

***MID Task Feedback Success Large Win vs. No Win Region of Interest Analysis***

Three regions of interest were selected; the anterior cingulate cortex, amygdala and mOFC. Due to the number of regions, and as no specific prediction was made regarding which hemisphere was most relevant, a Bonferroni correction for multiple comparison was applied and the threshold for significance adjusted to $p<0.008$. Test statistics for each region may be found in Appendix Chapter 6, Table 80 - Table 82. See Table 50 for a summary of the significant main and interaction effects for this contrast.

Table 48 Descriptive Statistics for the MID Task 'Feedback Success Large Win vs. Feedback No Win' Contrast Regions of Interest [Males Mean Beta Values (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| | **High CU (N=41)** | **Average CU (N=55)** | **High CU (N=83)** | **Average CU (N=309)** |
| **L ACC** | 0.28 (0.92) | 0.61 (1.08) | 0.38 (1.05) | 0.45 (1.06) |
| **R ACC** | 0.23 (0.75) | 0.37 (0.94) | 0.27 (0.86) | 0.30 (0.92) |
| **L AMYG** | -0.01 (1.42) | 0.1 (1.27) | 0.09 (1.05) | 0.09 (1.25) |
| **R AMYG** | 0.04 (1.11) | -0.03 (1.06) | -0.15 (0.90) | -0.09 (1.07) |
| **L mOFC** | 0.13 (1.29) | 0.36 (1.54) | 0.12 (1.36) | 0.31 (1.35) |
| **R mOFC** | 0.16 (0.97) | 0.32 (1.27) | 0.18 (1.14) | 0.22 (1.08) |

Table 49 Descriptive Statistics for the MID Task 'Feedback Success Large Win vs. Feedback No Win' Contrast Regions of Interest [Females Mean Beta Values (SD)]

| | CD | | CONTROL | |
|---|---|---|---|---|
| | **High CU (N=19)** | **Average CU (N=57)** | **High CU (N=31)** | **Average CU (N=441)** |
| **L ACC** | 0.34 (1.16) | 0.71 (0.79) | 0.25 (1.00) | 0.46 (0.92) |
| **R ACC** | 0.20 (0.92) | 0.52 (0.65) | 0.23 (0.80) | 0.30 (0.77) |
| **L AMYG** | 0.33 (1.27) | -0.03 (1.09) | -0.38 (1.56) | -0.04 (1.11) |
| **R AMYG** | 0.06 (1.05) | -0.00 (1.05) | -0.33 (1.15) | -0.00 (0.94) |
| **L mOFC** | 0.58 (1.16) | 0.41 (1.29) | -0.21 (1.11) | 0.25 (1.21) |
| **R mOFC** | 0.28 (0.79) | 0.28 (1.00) | -0.06 (0.75) | 0.22 (0.95) |

Table 50 Summary of Significant Main and Interaction Effects Region of Interest Analyses Feedback Success Large Win vs. Feedback No Win (MID Task)

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| L ACC | × | × | × | × |
| R ACC | × | × | × | × |
| L AMYG | × | × | × | × |
| R AMYG | × | × | × | × |
| L mOFC | × | × | × | × |
| R mOFC | × | × | × | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| L ACC | × | ✓ | × | |
| R ACC | × | × | × | |
| L AMYG | × | × | × | |
| R AMYG | × | × | × | |
| L mOFC | × | × | × | |
| R mOFC | × | × | × | |

***Main effect of CU***

There was a nominally significant main effect of CU in the left ACC in the full sample, however this effect did not survive correction for multiple comparison ($p$>0.008). The Average CU group showed a significantly larger BOLD response compared to the High CU group. There were no other significant main effects or interactions in BOLD response in any of the ROIs.

***MID Contrast: Feedback Failure Large Win vs. Feedback No Win Random Effects Analysis***

A one sample t-test was performed to identify brain regions significantly activated in the Feedback Failure Large Win vs. Failure No Win contrast. The summary statistical map was thresholded at $p$<0.05 (FWE; Family-Wise Error Corrected) and controlled for the effects of handedness, site and gender. Significant activation clusters were found in the orbitofrontal cortex, insula, anterior cingulate cortex and paracingulate gyrus, see Figure 26 and Table 51.

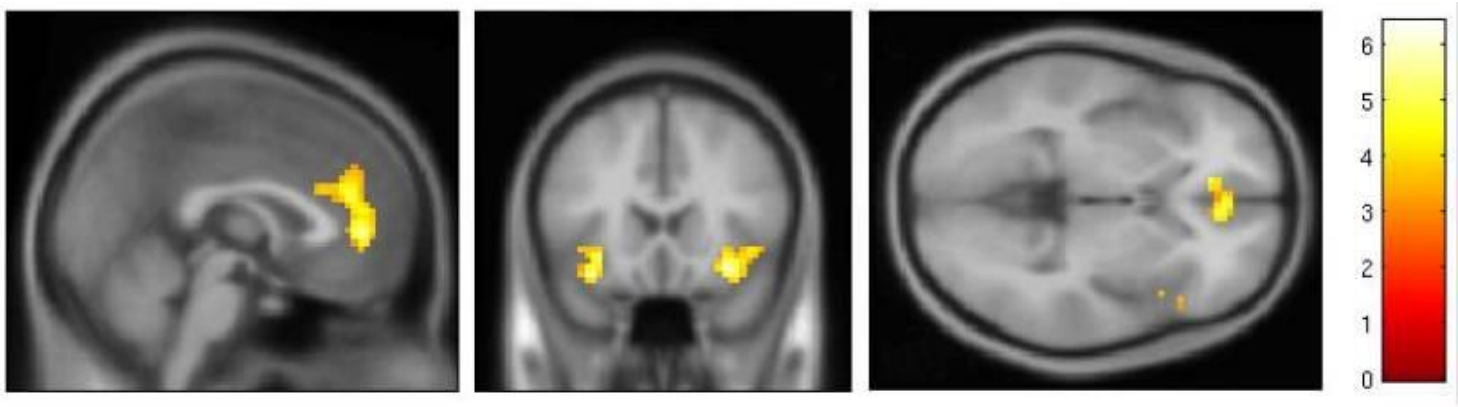


Figure 26 Random Effects Analysis Clusters for the MID Task 'Feedback Failure Large Win vs. Feedback No Win' Contrast (Full Sample)

Table 51 Significant Random Effects Clusters for the MID Task 'Feedback Failure Large Win vs. Feedback No Win' Contrast (Full Sample)

| | | | | | **Cluster** |
|---|---|---|---|---|---|
| **Brain Region of Activation (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Orbitofrontal Cortex, Insula | 47 | -33 17 -17 | 88 | 6.34 | $4.94^{-4}$ |
| Anterior Cingulate Cortex, Paracingulate Gyrus | 32 | 6 44 10 | 249 | 6.04 | $1.12^{-8}$ |
| Orbitofrontal Cortex, Insula, Inferior Frontal Gyrus (pars triangularis) | 45 | 30 20 -14 | 81 | 5.75 | 0.001 |

***MID Contrast: Feedback Failure Large Win vs. Feedback No Win Region of Interest Analysis***

Two regions of interest were selected; the anterior cingulate cortex and insula and the threshold for significance adjusted to 0.012. Test statistics can be found in Appendix Chapter 6, Table 83 and
Table 84. See Table 54 for a summary of significant main and interaction effects.

Table 52 Descriptive Statistics for the MID Task 'Feedback Failure Large Win vs. Feedback No Win' Contrast Regions of Interest in [Males Mean Beta Values (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| | **High CU (N=41)** | **Average CU (N=55)** | **High CU (N=83)** | **Average CU (N=309)** |
| **L ACC** | -0.06 (1.43) | 0.38 (1.75) | 0.45 (1.35) | 0.33 (1.41) |
| **R ACC** | -0.12 (1.22) | 0.23 (1.40) | 0.39 (1.12) | 0.25 (1.21) |
| **L INS** | 0.07 (1.09) | 0.08 (1.34) | 0.16 (1.21) | 0.14 (1.34) |
| **R INS** | 0.12 (1.12) | -0.03 (1.50) | 0.21 (1.36) | 0.06 (1.40) |

Table 53 Descriptive Statistics for the MID Task 'Feedback Failure Large Win vs. Feedback No Win' Contrast Regions of Interest in [Females Mean Beta Values (SD)]

| | **CD** | | **CONTROL** | |
|---|---|---|---|---|
| | **High CU (N=19)** | **Average CU (N=57)** | **High CU (N=31)** | **Average CU (N=441)** |
| **L ACC** | 0.66 (1.31) | 0.39 (1.50) | 0.13 (1.29) | 0.36 (1.42) |
| **R ACC** | 0.42 (1.00) | 0.26 (1.18) | 0.04 (0.80) | 0.29 (1.19) |
| **L INS** | 0.65 (1.03) | 0.02 (1.17) | -0.40 (0.89) | 0.11 (1.11) |
| **RINS** | 0.68 (1.36) | -0.02 (1.44) | -0.35 (1.11) | 0.10 (1.14) |

Table 54 Summary of Significant Main and Interaction Effects Region of Interest Analyses Feedback Failure Large Win vs. Feedback No Win (MID Task)

| **Interactions** | **Group-by-CU-by-Gender** | **Group-by-CU** | **Group-by-Gender** | **Gender-by-CU** |
|---|---|---|---|---|
| L ACC | × | × | × | × |
| R ACC | × | × | × | × |
| L INS | ✓ | ✓ | ✓ | × |
| R INS | ✓ | ✓ | ✓ | × |
| **Main Effects** | **Group** | **CU** | **Gender** | |
| L ACC | × | × | × | |
| R ACC | × | × | × | |
| L INS | × | × | × | |
| R INS | × | × | × | |

***Gender-by-Group-by-CU Interaction***

There was a nominally significant Gender-by-Group-by-CU interaction bilaterally in the insula (Left p = 0.023; Right p = 0.044), however these interaction effects did not survive correction for multiple region of interest analysis ($p$>0.012) and the effect size was small (Left eta$^2$ 0.005; Right eta$^2$ 0.004). In females with High CU there was a significant effect of group; females with CD and High CU showed significantly greater insula responses compared to control females with High CU. There was a strong trend in both the left and right insula for there also being a difference within the CD females, as a function of CU trait (CD High CU > CD Ave CU), however this effect was not quite significant (Left p = 0.050; Right p = 0.054). There were no significant post-hoc comparisons in the males (see Appendix Chapter 6, Figure 29 and Figure 30).

***Group-by-Gender Interaction***

There was a nominally significant Group-by-Gender interaction bilaterally in the insula (Left p=0.020, Right p=0.032), however the overall interaction effects also did not survive correction for multiple region of interest analysis ($p$>0.012) and the effect size was small (Left eta$^2$ 0.005; Right eta$^2$ 0.004). In both hemispheres it appeared as though females with CD problems were significantly more responsive in the insula bilaterally in comparison to female controls;

however formal tests did not show any significant differences between the groups. There were no significant effects in males.

***Group-by-CU Interaction***

There was a nominally significant Group-by-CU interaction bilaterally in the insula (Left p= 0.018, Right p= 0.022), however these effects did not survive correction for multiple region of interest analysis ($p$>0.012) and again the effect size was quite small (Left eta$^2$ 0.005; Right eta$^2$ 0.005). Within the group of adolescents with CD problems, those with High CU traits showed significantly greater insula responses compared to the CD group with Average CU traits; however formal tests did not show any significant differences between the groups.

## 6.5 **Discussion**

*This study investigated hot executive processes of risky decision making and incentive sensitivity that have previously been shown to be impaired in individuals with CD problems with and without CU traits. Contrary to previous reports no significant differences were found between the CD and Control groups for risk taking behaviour, although there was a significant main effect of gender; males showed significantly greater risk taking tendencies compared to females. In terms of neurofunctional reactivity there were only nominally significant effects that did not survive correction for multiple comparison. During the anticipation of reward males with High CU showed significantly greater BOLD responses in the left ventral striatum compared to Males with Low CU. In the outcome phase when participants were notified they had won a large reward, adolescents with High CU showed significantly greater responses in the anterior cingulate cortex. During the notification of a failure to receive a reward there were nominally significant interactions between the CU trait, gender and diagnosis bilaterally in the*

*insula. Females with CD problems and High CU traits showed significantly greater BOLD responses compared to control females with High CU.*

***Males take significantly more risks compared to females in a gambling task***

Consistent with the findings presented in the introduction of this chapter (Cloninger *et al*, 1991; Romer & Hennessy, 2007) there was an overall main effect of gender; males made significantly more risky decisions compared to females, wagering a greater proportion of their total across both measures; overall and when the 'odds' were in their favour. This finding is in direct contradiction to a recent review of sex differences in decision making (van den Bos, Homberg, & de Visser, 2013) which found no significant sex-differences across various gambling and risk taking paradigms. However this could be a consequence of the samples reviewed; the review considered adult data while this study worked with adolescents. It is plausible that during adolescence males are more likely to engage in risk taking behaviours while females are more cautious, putting males at greater risk for the development of hazardous behaviour such as substance use. This may go some way to accounting for the sex-differences in prevalence estimates of young adults with substance use problems; a significantly greater number of males are affected compared to females (Seedat *et al.,*2009).

It was predicted that the adolescents with CD would show a greater propensity for risk taking by making greater wagers overall, and in circumstances where the odds seemed more in their favour, compared to the control adolescents. This study found no evidence to support this hypothesis; the CD and control groups made equally risky decisions. It was also predicted that the CU trait would be associated with a reward-dominant style, as suggested by O'Brien and Frick (1996), however no such effect was found. It is possible that the youths with CD and those with High CU in this study did not find the task sufficiently motivating to observe any

significant differences between the groups as a function of CD or CU. It would be fruitful to investigate this effect further, especially as it was unexpected, by examining the kinds of risk taking behaviours shown following losses as the task progresses, to observe whether there is an effect of learning, or perhaps of punishment. The rationale for this approach is based on the findings of Fairchild *et al.,*(2009) and Syngelaki *et al.,*(2009), who found that youths with CD wagered larger sums on gambling tasks following the receipt of small rewards, and showed a preference for large rewards despite being penalised (Luman *et al.,*2010). Perhaps the variable was not quite sensitive enough to detect differences in risk taking behaviours between CD and Control adolescents in this particular study.

***Conduct Disorder problems, Callous Unemotional traits and the Neural Basis of Reward Anticipation***

Consistent with previous reports there was no main effect of Group during reward anticipation (Bjork *et al.,*2010), neither was there a significant moderation of this effect by CU traits or, in contradiction to previous findings, by gender. This study did find some evidence to suggest that the 'reward-dominance' associated with CU traits may be moderated by gender during reward anticipation. Consistent with the report by Buckholtz and colleagues (2010) this study found a nominally significant interaction effect in the left ventral striatum. Males (but not females) with High CU showed significantly greater response in the left ventral striatum compared to males with Average CU. Greater sensitivity to the anticipation of reward in males with High CU compared to males with Average CU may reflect the reward dominant style proposed by O'Brien and Frick (1996) associated with an overactive Behavioural Activation/Reward System. In practical terms, this increased sensitivity to a possible reward may go forth somewhat to explain why individuals with high levels of this trait engage in disadvantageous behaviour for personal gain, despite the negative consequences for other individuals. This gender-specific effect might reflect differences in motivation for males and

females as suggested by Spreckelmeyer *et al.,*(2009), the authors found that females are more driven by socially rewarding stimuli rather than monetary. A potentially useful further study would therefore be to investigate the extent to which CU traits moderate the responses of the neural reward system in females in a socially rewarding as well as during monetary rewarding condition.

***Conduct Disorder problems Callous Unemotional traits and the Neural Basis of Positive Reward Notification***

It was predicted that the notification of a large reward would be associated with increased responses of all three regions of interest in adolescents with CD compared to controls; however this study found there were no significant differences between the groups. It had been expected that hypersensitivity to reward would be characteristic of this group however this was not the case in line with the findings of (Gatzke-Kopp *et al.,*2009).

The present study found a nominally significant effect refuting the prediction that High CU would be associated with a reward-oriented style and would therefore be associated with greater activation in the ROIs during the notification of received reward. Overall, the Average CU group showed significantly greater activation in the anterior cingulate cortex (ACC) compared to the High CU group. The ACC has been shown to be important for the representation of reward magnitude (Rogers *et al.,*2004), suggesting that it has an important role in reward based decision making. While this effect went in the opposite direction to that which it was expected, it does support the findings of Centifanti and Modecki (2013), who presented evidence suggesting that individuals with High CU are less sensitive to accruing rewards. The ACC shares connections with areas of the mPFC that supervise or monitor behaviour. Therefore if this particular area is dysfunctional in individuals with High CU,

evidenced by reduced responding during the notification of successful reward, it might mean that weak signals regarding the representation of reward are sent to the mPFC. This might lead to an underrepresentation of reward that in turn leads to sub-optimal choices being made, as the individual may not be able to represent rewarding options, and so instead of making considered decisions, may engage in detrimental behaviours to raise the activity of their underactive reward related regions.

***Conduct Disorder problems, Callous Unemotional traits and the Neural Basis of Negative Reward Notification***

Overall there was no main effect of Group, consistent with the findings of Gatzke-Kopp *et al* (2009). The present study did find some evidence that CU was associated with aberrant processing of negative reward outcome, and that these effects were sex-specific. There was a nominally significant effect bilaterally in the insula; CD females with High CU showed significantly greater BOLD response in the left and right insula compared to control females with High CU, there was no such effect in males. In a review of the literature, Mohr and colleagues (2010) found that the insula was activated for risk processing, particularly during the decision making phase and the anticipation of risk, but was also activated when the participants were confronted by potential losses. In addition to risk processing the insula is involved in processing aversive emotions (see Paulus and Stein, 2006). It is possible that the reactivity elicited by this task is an emotional response to the notification of no gain, which could have manifested as disappointment or frustration. In this contrast significant insula activation might be evidence that participants may be showing an emotional reaction to the notification that they have not achieved their goal (to win points) where they were expecting to. However this explanation is speculative as no emotional rating data were taken from the participants concerning how they felt following notifications of rewards or misses for different values. It could be that this group - the CD females with High CU - have a heightened sensitivity

to punishment. This finding could be considered consistent with the findings of Centifanti and Modecki (2013) who found that following punishment, females with High CU were slower to take risks and were slower to respond. A future direction could therefore examine whether females with High CU responded slower to the next target after the notification that the reward was missed, perhaps making more errors than their average/low CU counterparts. This would be necessary to determine the extent to which this effect is unique to females, rather than males.

Unusually there were no significant differences detected between the CD and control groups for any stage of reward processing; there were no significant main effects. This finding was not expected; however when one reviews and collates the findings of other research groups, it is not unusual. Bjork *et al.,*(2010) found no significant differences in reward anticipation reactivity, Gatzke-Kopp *et al.,*(2009) found no significant differences in reactivity during negative outcome feedback, and neither did they find any significant differences in reactivity during positive reward feedback. It is possible that a different analysis strategy will need to be taken to further examine this effect. In the investigation of Gatzke-Kopp *et al.,*(2009) the authors investigated both region of interest and whole brain reactivity. Instead of finding clear-cut differences in the between-group analyses they found a shift in the pattern of reactivity; so the areas that were recruited during each phase of reward processing differed between the externalising youths and controls. In their externalising group they found that during non-reward the externalising group continued to show activation in the striatum, rather than shifting activity to the anterior cingulate cortex as the control group did. It is possible that the approach used in this thesis was not sufficient to fully characterise reward processing in this group and suggests that exploratory whole brain analyses would have been extremely beneficial to understand better the reactivity patterns across the brain.

*Limitations*

This study could have also been improved by the inclusion of behavioural ratings following the notification of reward success or failure. Behavioural ratings would have meant that frustration, disappointment or annoyance at not receiving a reward when expecting one could have been more thoroughly explored. It would have also been preferable to have included a social in addition to monetary reward condition in the fMRI paradigm. This is particularly pertinent when investigating gender differences in reward processing; as previous research has indicated, females respond preferentially to social rewards, while males are more driven by monetary rewards.

*Conclusions*

This study provides additional evidence that CU traits are associated with a reward dominant neurofunctional profile during the anticipation of large rewards, and suggests that during the anticipation of reward this effect is specific to males. Contrary to previous reports CD problems were not independently associated with a particular bias toward the anticipation or notification of reward in males or females. During the notification of no reward there was a nominally significant trend suggesting that females who have CD problems and High CU traits may be more sensitive to negative outcomes, or punishment, compared to Control females with High CU traits. These finding could have potentially useful treatment implications. For instance interventions that focus on rewarding positive behaviour rather than punishing negative behaviour might have more success with tangible behaviour change. These results also suggest that using gender specific targeted interventions might also have some utility, however the extent to which females with High CU and CD problems truly are punishment sensitive would need to be explored further.

# Chapter 7 General Discussion

The research review by Moffitt and colleagues (2008), referred to in the Introduction of this thesis, identified priority research areas fundamental for our understanding of conduct disorder problems. The authors identified themes related to the assessment and diagnosis of conduct disorders which included and were not limited to (i) the use of callous unemotional traits as a subtype for CD, the utility of biomarkers for the classification of CD including; (ii) neuroimaging phenotypes, and (iii) the exploration of CD symptom manifestation and associated difficulties in females.

The overarching research aim of this project was to investigate the extent to which males and females with conduct disorder problems were similar to one another in terms of clinical, temperamental and executive and neurobiological function. Many studies have been unable to make direct comparisons between males and females with CD due to study limitations such as sample size. This thesis worked with one of the largest imaging datasets in Europe and so was able to make direct comparisons between males and females with CD problems. An additional aim of this thesis was to not only characterise CU traits in terms of CD, but also to investigate typically developing individuals without CD symptoms who also have high levels of CU.

Four empirical studies were conducted in a cohort of community recruited adolescents. All investigated first the similarities between males and females, and then the extent to which callous unemotional traits delineated a sub-group of individuals for whom clinical symptom counts were exacerbated, or performance appeared to indicate function was worse. The first study investigated the clinical and temperamental profile of the cohort at age 14 and 16, with a specific focus on externalising and internalising clinical symptoms and traits. The next study explored emotional reactivity using an fMRI paradigm, depicting negative emotionality (angry faces), and examined whether neurofunctional reactivity varied across the cohort. 'Cool' and

'Hot' executive function were explored in two separate studies. 'Cool' cognitive executive function was assessed through neuropsychological measures of working memory, and neurobiological evidence of inhibitory control through a stop-signal fMRI paradigm. 'Hot' (motivational) executive function was assessed through a gambling task and the neurobiological sensitivity to reward was explored through a monetary incentive delay fMRI paradigm.

The findings from these studies are discussed in sections 7.1 - 0 in relation to the overarching research questions; (i) Are males and females with conduct disorder problems the same as one another?, (ii) Do callous unemotional traits delineate a sub group of individuals with a different profile to their peers?, and (iii) Do CU traits interact with gender or CD problems?

## 7.1 Are males and females with Conduct Disorder problems the same as one another?

**Yes – Behavioural Similarities**

To an extent, the evidence suggests that males and females with CD problems do show similar clinical, temperamental and neuropsychological profiles to each other. In terms of externalising symptoms this investigation found that CD was associated with increased symptoms of hyperactivity/inattention in both males and females, consistent with other reports (van Lier *et al.,*2003; Waschbusch, 2003; Frick *et al.,*2003), and while gender did not moderate the effect of CD on hyperactivity/inattention symptoms there was an overall gender effect; males showed greater symptoms of hyperactivity/inattention compared to females. Males and females with CD showed greater levels of trait impulsivity, and also experienced greater peer relationship difficulties compared to the control group. These findings are supportive of the proposition that youths with CD problems show a tendency toward a disinhibited temperamental style that might put them at risk for engaging in negative

behaviours such as bullying or acting without thinking, which may in turn put them at risk for developing co-occurring symptoms of internalising problems.

Consistent with the reports of Maughan *et al.,*(2004), and Polier *et al.,*(2012) this study found that both males and females were equally affected by internalising symptoms; emotional problems and a personality trait measuring negative emotionality (hopelessness). There was also a significant main effect of gender for both of these measures; females reported being more affected compared to males, supporting the finding of Cukrowicz *et al.,*(2009). In terms of implications this study demonstrates that adolescents with CD problems show many traits indicative of both externalising and internalising difficulties, which may complicate their symptom profile. In terms of the degree of similarity between males and females, this has been noted before by Maughan *et al.,*(2004), who only found gender differences in the type of CD behaviours the children and adolescents showed, such as breaking and entering for theft and cruelty to animals. While no gender differences were found in this study in terms of symptom characteristics, the possibility that there may be differences in the types of aggressive and delinquent behaviour exhibited by the adolescents was not investigated. As a future aim one might explore the patterns of bullying behaviour, of delinquent acts such as truancy, and of negative behaviours such as substance use and risky sexual behaviour.

In terms of 'cool' executive function there was no evidence to suggest that males and females with conduct disorder problems performed significantly differently to one another on the neuropsychological tasks, both showed significantly worse working memory ability compared to control subjects. This is one of the first studies to investigate the performance of both males and females on cool EF tasks in the same study, which is novel. Cool EF ability has been measured extensively in youths with CD problems, however some of the previous investigations have been limited by their inability to adequately control for between group

differences in IQ, and also for the contribution of ADHD symptoms. This study was particularly useful as it allowed for the exploration of the contribution of both of these variables, and meant the study was able to demonstrate what appeared to be core deficits associated with CD problems. It appears that consistent with previous research (Syngelaki *et al.,*2009; Barnett *et al.,*2009; Cauffman *et al.,*2005), working memory problems are characteristic of youths with CD problems. This is particularly interesting as it might help explain why this group struggle to plan ahead, as reported by Dolan and Lennox (2013), which might mean that they become more driven by their immediate environment, or dependent on rewards or incentives. Further work to explore more fully the relationship between working memory and planning would be a really useful way to explore this proposition.

In terms of hot EF measures of risk taking and incentive processing there was no significant main effect of CD problems, although there was a significant main effect of gender; males showed significantly greater risk taking behaviour compared to females. There is a possibility that as the group moves through adolescence both males and females CD will go on to develop greater risk taking behaviours; for instance substance use initiation, or risky sexual behaviour. It may be that the CD group do show greater risk taking, but this might be evidenced by more real-life behaviours, rather than one simulated in a laboratory. Such a proposition would need to be investigated longitudinally. In terms of neural reactivity there were no significant differences between the responses of males and females with CD during reward anticipation, consistent with the report of Bjork *et al.,*(2010), however there were trends towards significant differences in their responses during reward notification, these effects are discussed in more detail in the following section.

**No – Different Neural Activation**

There is a wealth of evidence documenting the differences in regional brain activation between typically developing males and females across the lifespan in terms of emotional reactivity and a growing evidence base for gender differences in response inhibition, however thus far there have been no studies of sufficient power that have examined gender differences in brain activation within conduct disorder. This thesis found evidence to suggest there may be significant differences between males and females with CD problems at the neurobiological level.

In the emotional reactivity paradigm it was found that while BOLD response in the amygdala varied according to group in males (CD males showed significantly lower BOLD responses compared to control males), there was no such effect in females. As discussed in Chapter 4, it is possible that males and females are 'biologically hardwired' to respond to threatening stimuli in different ways and that the aberrant function of CD in males may be a consequence of faulty stimulus-reinforcement learning. The research presented in Chapter 4 of this thesis showed that, consistent with previous findings (e.g. Passamonti *et al.,*2010), reduced amygdala function in response to angry faces may be a core characteristic of males with CD problems. While behavioural emotion recognition paradigms suggested that this is also a feature of females with CD problems, in this study reactivity did not vary in females according to group. As suggested by Fairchild and colleagues (2009), this finding appears counterintuitive. However the notion or proposition that this group of adolescents show a tendency for a reduced sensitivity to signals of punishment or aggression appears might make good sense. The amygdala participates in part of a neural circuit moderating aggressive behaviour, and so if CD problems are associated with difficulties in reinforcement learning, and have reduced amygdala function, they might have a reduced capacity to learn the properties of reinforcing behaviour such as punishment. This may help explain why this group persist with negative

behaviours, despite being punished. Interestingly there were no significant differences in females with CD compared to female controls, suggesting at least in this paradigm, during the display of anger, females with CD problems do not show a significantly different pattern of neural reactivity.

There was also a significant difference in neural response in males and females with CD problems in the stop signal inhibitory control paradigm. Reactivity in the inferior frontal gyrus related to successful response inhibition did not vary according to group in males or females; however there was a significant difference in the magnitude of the BOLD response within the CD group as a function of gender. Males with CD showed significantly greater BOLD responses compared to females with CD; an effect not found in the control adolescents. It was postulated that males and females with CD problems show different patterns in the magnitude of neural resources required to inhibit their responses due to differences in cortical maturity, however this notion would need to be explored experimentally to confirm such a hypothesis. The finding that males with CD showed significantly greater reactivity compared to females during the response inhibition paradigm is novel. There have been no previous investigations into gender differences in the neural response to inhibitory control in adolescents with CD before, although the same gender difference has been found in a typically developing group of adults (Li *et al,* 2006; Li *et al,* 2009). The possible implications of these findings are discussed in the following section.

In order to explore fully the origins of neurofunctional differences between males and females with CD problems, there are a range of studies upon which one might embark. One could comprehensively address the possibility that males and females with CD might differ in terms of neural reactivity to emotional material by exposing them to a task containing both positive and negative emotional stimuli and systematically exploring the extent to which reactivity

across the brain varies compared to each other, and also to a control group of males and females.

In addition to differences in functional activation it would be pertinent to investigate the extent to which males and females with CD problems show differences in brain morphometry; that way functional activation differences can be discussed in light of anatomical differences between the groups. This would make sense in terms of examining brain regions identified from both the emotional reactivity and inhibitory control paradigms. Morphometric differences in males and females with CD were recently presented by Fairchild and colleagues (2012); so as a first attempt to replicate this finding one could use data available from the Imagen dataset to explore the extent to which males and females with CD show differences in anatomical structure to one another.

## 7.2 Do callous unemotional traits delineate a subgroup of individuals with a different clinical, neuropsychological, temperamental, or neural reactivity profile?

In the Introduction to this thesis one of the first studies to highlight the importance of assessing CU traits was discussed. Christian and colleagues (1997) found that High CU traits in the absence of CD problems were associated with significant difficulty at school, increasing the risk of suspension in this group. A great deal of research has since focused on understanding more about the differences between groups of children with CD problems who have and do not have high CU traits. However since this initial study, less attention has been paid to the significant difficulty high CU also poses for typically developing children. This thesis addressed this by investigating the extent to which CU traits delineated a sub-group of individuals with and without CD who showed a different clinical, neuropsychological, temperamental or neural reactivity profile across the cohort.

**Yes, CU traits do identify a sub group of controls who seem different at both the behavioural and neurobiological level**

In terms of clinical and temperamental phenotypes High CU was associated with significantly greater peer relationship difficulties, higher trait impulsivity and greater negative emotionality across the cohort (not delineating by CD status) at age 14, and significantly lower empathic concern scores at age 16. These findings are consistent with the proposition of Frick and colleagues (2003), who suggested that CU traits are associated with behavioural dysregulation that manifests as externalising behaviours such as peer relationship difficulties and trait impulsivity. This investigation has extended the findings of Frick and colleagues by also presenting evidence that CU traits may also be accompanied by greater negative emotionality, a dispositional trait indexing negative affect (Hopelessness). At age 16 adolescents with High CU also showed less empathic concern compared to their peers with average CU. While there was a significant main effect of CU on these variables it is interesting to note that there was no interaction effect; CU did not allow for the identification of Control or CD adolescents for whom High CU resulted in significantly greater symptom impairment when subjected to statistical tests. An interaction effect was however observed between CU and Group in relation to symptoms of hyperactivity/inattention. Closer examination of these effects revealed that while CU did not moderate the relationship between CD and hyperactivity/inattention, High CU was associated with significantly greater symptoms compared to those with only Average CU in the Control group. There was also a significant interaction between Gender and CU traits; males with High CU showed significantly greater symptoms of hyperactivity/inattention compared to those with Average CU, however there was no such effect in females.

These findings are very interesting, given that they are found in adolescents who do not have CD problems. Taken together they suggest that CU may act as a general independent risk

factor for the development of externalising and internalising symptoms which may significantly affect the wellbeing of the adolescent. The findings also suggest that CU is associated with low behavioural inhibition and poor emotional resonance with peers; this may mean that the youth is not able to adequately regulate their behaviour and may engage in antisocial, undesirable activities. While the effect sizes are small they may still be indicative of possible risks for the development of more damaging behaviour as the adolescent gets older. Evidence presented by Wymbs *et al.,*(2012) in the Introduction showed that CU is associated with substance use during adolescence. It is entirely possible that the adolescents with High CU are at greater risk compared to their peers for experimenting with substances, and perhaps as they get older these co-occurring externalising and internalising traits become more stable, which in turn would be negative for the adolescent.

In terms of neural reactivity, there was an interesting effect in the basal ganglia during the emotional reactivity task. Overall, individuals with High CU (both CD and Control) showed significantly greater reactivity in response to angry emotional faces compared to the Average CU group. There was also a significant interaction between gender and CU, in that females with High CU showed significantly greater responses compared to females with Average CU. This was an unexpected finding but may help to explain why this group engage in negative behaviours. It is possible that the CU group perceive an angry face as a challenge to their dominance and show an exaggerated neural response, which may motivate engagement in aggressive behaviours. This assertion is possible, however it must be taken in the context of the three-way interaction effect that was also found, which suggests that while males with High CU might view an angry face as a challenge to his authority, an angry face might mean something different for females with High CU. This is discussed in more detail in section 0.

There were also two potentially very interesting, although only nominally significant, associations between CU and neurofunctional reactivity in the reward processing fMRI paradigm. During the anticipation of reward, males with High CU showed significantly greater BOLD responses in the ventral striatum, a key reward region, compared to males with Average CU, an effect that did not occur in females. A similar effect was shown by Buckholtz and colleagues (2010), who found in a community recruited sample of volunteers that impulsive antisocial personality traits were associated with increases in nucleus accumbens response (part of the ventral striatum) during the anticipation of reward. A more recent study by Bjork and colleagues (2012) replicated this effect; also finding that in a community sample, trait psychopathy was associated with increased neural response in the ventral striatum and anterior cingulate cortex during reward anticipation. These findings appear at odds to the effect then found during the feedback phase of the task presented in this thesis. Instead of showing a significantly larger response to the receipt of reward, as reported by Bjork et al (2013), this thesis presented evidence showing the opposite effect. High CU was associated with significantly lower responses in the anterior cingulate cortex (ACC).

The results presented in this thesis are more compatible with those of Finger and colleagues (2011), albeit in a different region of interest. The authors showed that youths with CD/ODD and high psychopathic traits showed disruption (less reactivity compared to controls) in areas important for value representation and reward processing; the orbitofrontal cortex and caudate. The ACC is an area also important for value representation and processing punishment, and has been shown to function aberrantly in children with CD/CD+ADHD (although CU traits were not indexed), in that during a reward omission the ACC was not recruited in these adolescents (Gatzke-Kopp *et al.,*2009). These results suggest that while CU (in both CD and Control subjects) might be associated with a reward-oriented style during anticipation, the notification or receipt of reward is actually less gratifying or rewarding. This

might help to explain why this group (High CU), persist with negative behaviours despite achieving a rewarding goals.

The results presented here partially support the notion that High CU is associated with a reward-oriented style, but also go further and suggest that this might be more specific to males. The findings of both tasks suggest that there might be a gender disparity in the underlying neurobiology of conduct disorder problems. The results presented in this thesis provide preliminary evidence to suggest that while males behave in the classically reward oriented, punishment insensitive manner as described by the Behaviour Activation System Theory of Gray (1990) and the Reward-Overactivity hypothesis of Ernst *et al.,*(2006), females appear to show a heightened sensitivity to punishment and are less reward oriented than their male peers. However, despite the novelty of this finding in females, the effects in the MID task were only nominally significant and did not survive statistical correction for multiple comparisons; therefore little weight may be given to them until replicated.

**No, CU traits do not identify a group of individuals who seem different**

A previous investigation by Frick and colleagues (2003) reported that CU traits allowed for the distinction of a sub-group of CD individuals for whom externalising symptoms were worse. This investigation failed to replicate such an effect. This is perhaps a consequence of working with a group of community recruited adolescents who had above average levels of CD problems compared to their peers; it might be that such an effect is only present in groups who have clinically significant levels of CD problems.

There were no main or interaction effects of CU on neurofunctional reactivity of the amygdala during the emotional reactivity task or during the stop-signal inhibitory control task. It had

been predicted that CU might have an effect on BOLD response in the amygdala; however, consistent with the findings of Passamonti *et al.,*(2010), this was not the case. This study was one of the few to investigate the effect of CU traits on neurofunctional response to anger in both males and females; CU traits did not modulate neural reactivity to angry face stimuli in the amygdala in the same manner as has been reported in CD youths for fearful face stimuli. This suggests that the previously reported amygdala dysfunctions in this group may be more specific to stimuli signalling distress (e.g. fear or sadness) rather than one signalling aggression. There were also no significant effects of CU traits on cool executive function abilities; the relationship between CU and executive function appears to be distinctly associated with affective or motivation problems as shown in Chapter 6.

Collectively these results suggest that CU traits moderate clinical symptom manifestation and personality traits, and also neurofunctional reactivity in response to angry faces in areas of the brain related to reward processing, and nominally for anticipated and received rewards, which may represent different responses to rewarding and punishing stimuli in males and females.

## 7.3 Do CU and Gender interact to moderate any of the similarities or differences between males and females with CD?

The final question this thesis addressed was the extent to which CU traits and gender interacted to moderate some of the relationships between the outcome phenotypes of interest in males and females with and without CD problems.

**Yes, CU and Gender do interact to moderate the differences between males and females with CD for clinical symptoms, temperamental traits and neurofunctional responses to rewarding stimuli**

One of the most interesting findings was a significant CD-by-Gender-by-CU interaction for internalising symptoms (emotional problems and negative emotionality). Control females with High CU traits reported significantly more internalising symptoms than those with Average CU; no such effect was observed in females with CD problems. Males (with and without CD problems) with High CU showed a similar pattern to the females, but the effect was isolated to the negative emotionality dimension, not the clinical symptom measure. Critically, these findings provide preliminary evidence suggesting that CU traits alone may be sufficient to identify adolescents at risk for developing significant internalising symptoms associated with negative affect. It is also possible that CU traits may confer a separate liability for the development of internalising symptoms; particularly if the person is female, however a longitudinal assessment of these individuals would be required before making more concrete assertions.

There was also a potentially interesting effect found in neurofunctional responses to the omission of an expected reward. There was marginally significant evidence to suggest that females with CD problems and High CU might be punishment sensitive, rather than insensitive as the literature had suggested. A significantly greater response in the bilateral insula in

response to the omission of reward was found in females with CD problems and High CU compared to control females with High CU. This finding is potentially very interesting as the insula has been shown to process the aversive part of a response (Paulus *et al.,*2003; Paulus and Stein, 2006). This is suggestive that females with CD and High CU show an exaggerated, rather than blunted response to punishment, one that may have an aversive affective component. While care must be taken not to over-emphasise the effect, which did not survive correction for multiple comparison, it might help form the basis of future research questions. For instance one could design an fMRI study akin to the gambling paradigm used by Centifanti and Modecki (2013). However, it would also be interesting to investigate sensitivity to non-social (monetary) and social (smiling/angry faces) rewards and punishments to explore the extent to which reactivity across adolescents with and without CD and CU traits varies according to gender. This would mean that one could explore the domains across which this group is sensitive to punishment. This thesis has already provided some tentative evidence that females with High CU (both CD and Control) are more sensitive to negative emotional stimuli (angry faces). If further evidence was found supporting this tentative finding of punishment hypersensitivity, then this could have important implications for treatment interventions, suggesting that sex-specific targeted interventions might be not only preferable, but also necessary.

**Why is measuring CU traits important, especially in adolescents without CD problems?**

To date, researchers have made great gains in understanding more about the etiology (Barker *et al.,*2011; Fontaine *et al.,*2010; Cornell & Frick, 2007) and long term outcomes of co-occurring CD problems and CU traits (Pardini et al, 2010). CU only does not currently exist as a classifier for clinically significant levels of behaviour, so one might query why this thesis investigated a group of CU only adolescents who did not have significant levels of CD Problems. A recent editorial by Viding and McCrory (2012) highlighted the importance of

measuring CU traits in children, concluding that CU traits might be of clinical significance, even when they occur in the absence of antisocial behaviour problems.

Previous research has found that children with CU only showed significant risk for the development of CD problems (Barker *et al.,*2011). Frick *et al.,*(2003) found that children with CU traits without CD problems showed low behavioural inhibition, and more recently Pardini *et al.,*(2012) examined the extent to which females with CU traits without CD problems were at risk for later maladaptive outcomes and found supporting evidence that they were at greater risk for the development of disinhibited behaviours (ADHD, ODD). Fontaine and colleagues (2010) also provide evidence suggesting that CU, even given its instability (CU can increase/decrease over time), represents a clinical marker for the risk of adjustment problems in early adolescence. The authors showed that CU was associated with greater levels of behavioural problems and family risk factors. Finally, evidence from Munoz *et al.,*(2010) showed that high CU traits in a group of community recruited children showed the lowest affective empathy (comparable to empathic concern) and also showed high direct bullying behaviour. The researchers also showed that CU traits were the single most important predictor of bullying, more so than simply a lack of empathy.

Learning about the negative outcomes in a group of children/adolescents who do not have CD problems, but as a consequence of CU traits is therefore important for a number of reasons. It suggests that those behaviours common to children with behavioural problems (CD) may not be unique to them, which leads one to question why these children do not go on to develop CD problems. It is possible that these children may be exposed to protective elements in the family home that preclude the development of overt CD problems. Similarly, it is also possible that these children may represent a delayed group who do go on to develop CD problems, but later in life.

In this thesis adolescents with High CU showed elevated levels of internalising symptoms associated with depressive behaviour (emotional symptoms and negative thinking/hopelessness), supporting the notion that these children may be at greater risk for the development of other types of psychopathology (Salekin, Rosenbaum, Lee, & Lester, 2009). Additionally this thesis investigated the neurocognitive profile of these adolescents. They showed no differences in performance on the neuropsychological measures in this investigation, however there was evidence presented here that hints towards some subtle differences in neurobiological function. The preliminary evidence presented here suggests that in response to angry moving faces that they show different patterns of reactivity in an area of the brain that plays a role in anger processing and the representation of reward, and also evidence to suggest that adolescents with High CU might respond differently to the notification of a large reward, in an area of the brain important for value representation. This represents an important contribution to the burgeoning literature suggesting that CU traits might be associated with particular neural signatures. This thesis underlines the necessity of conducting longitudinal studies across development from childhood, through adolescence and into young adulthood to further investigate the temporal stability of the CU trait and the associated clinical and temperamental outcome, and also emphasises the importance of assessing the neuropsychological and neurofunctional profiles of these individuals.

## 7.4 **Limitations and Future Directions**

This section reviews some of the limitations of this thesis and offers some plans for how the studies presented might be improved and expanded in the future.

*Studying male and female adolescents with Conduct Disorder Problems*

Adolescence is a critical period for social, physical and cognitive development (Choudhury, Blakemore, & Charman, 2006). It is a period of increased risk taking, poor decision making and

antisocial behaviours that put the individual at risk for the development of substance use and other maladaptive behaviours (Casey, Getz, & Galvan, 2008). As adolescence is such a critical period in development it is an appropriate developmental milestone to assess the extent to which clinical and personality traits help to form the basis for a physically and mentally healthy adult life. One of the particular strengths of this thesis was the large sample size which meant that variation between males and females with CD problems could be investigated systematically.

*Categorical or Continuous Trait Classification?*

The notion of whether mental health problems, or indeed any traits, can or should be categorised is contentious. In a recent review of this debate Coghill and Sonuga-Barke (2012) assessed the methods through which child and adolescent mental health problems are best classified. In terms of categorical diagnosis, the authors proposed that would mean that mental disorders are "qualitatively different from variation across the normal range of expression in the population". This is very different to the dimensional approach to classification that regards mental health problems as "an extreme expression of normal variation in the population" (Coghill & Sonuga-Barke, 2012).

The categorical approach to the classification of participants in this thesis could therefore be considered a methodological limitation. The categorical approach was favoured as any significant effects could be discussed and interpreted in terms of existing research findings of CD clinical groups. One future aim would therefore be to repeat these analyses using symptom count scores to explore the extent to which using a dimensional approach might better detect subtle deviations from normality in the cohort as a whole, and would increase the ability to detect the effects of extreme and sub clinical traits across the population. This approach has been used by two different research groups alongside analysis of categorical groups to great

effect (Pardini *et al.,*2012; Hobson, Scott & Rubia, 2011). In particular the dimensional approach allows one to explore more sensitively the independent contribution of additional factors such as symptoms of ADHD on the outcome phenotypes of interest. This would allow one to determine what traits (CD/ADHD) are specifically associated with deficits across the tasks and also clinical symptom type.

There is an emerging body of evidence suggesting that the dimensional approach is often superior when predicting outcome. Fergusson and colleagues (2010) investigated the predictive validity of categorical and continuous classifications for all three disruptive behaviour disorders; Conduct Disorder, Oppositional Defiant Disorder and Attention Deficit Hyperactivity Disorder. They found that predictive power varied as a function of the approach and found that their scale score model consistently outperformed the categorical model in terms of capacity to predict later outcomes. For example, they found that variance estimates for conduct disorder using the scale score model were between 0.6% - 20% (median 6.5%), while the categorical estimate was much lower, ranging from 0.2% to 11.3% (median of 3.2%). Across the three disorders the authors found that estimates of the proportion of variance explained by the categorical classification were half of that found by the dimensional scores. The authors suggest that the scale score method takes into account the severity of the disorder, which allows a more accurate prediction.

Overall, as prediction was not the aim of this thesis, using the categorical classification was by and large an appropriate approach. It meant that findings could be discussed in light of existing research using groups classified by above/below threshold scores of clinical diagnosis. One future Imagen analysis plan related to this thesis will be to examine the relationships between the CD, CU and the dependent variables across the dataset at age 14 and age 16 consistent with the approaches used by Pardini and colleagues (2012). This will mean that the predictive

validity of these traits can be assessed using both between-group and dimensional approaches in both males and females within the Imagen sample. These data were not initially available when this thesis was being written however they will be imminently.

*Imagen Sample*

The Imagen dataset is extremely rich in terms of available data and was one of the first large-scale imaging-genetics investigations in Europe. The clinical, personality and neuropsychological measures used in this thesis were all well-validated for use in different languages and for use with community samples, as has been discussed in the methodological and empirical chapters. However, while the assessment battery was comprehensive it did not contain the optimal measures to fully address some of the current research questions. For instance, it would have been preferable to have used one of the widely available validated measures of CU traits such as the Antisocial Process Screening Device (APSD; Frick & Hare, 2001) rather than having to infer CU using a proxy scale. One particular methodological limitation related to the use of a non-validated measure was the lack of multi-informant ratings. It would have been preferable for the parent of the adolescent to provide ratings of CU, however as the measure was developed using the Dadds *et al.,*(2005) model with additional items to increase the similarity to their outcome measure it was simply not possible to use parent ratings.

One disadvantage of the approach used in this study was the inability to separate the CD group in terms of age of onset. As the Imagen participants were community recruited, adolescents were classified as having conduct disorder problems or as controls on the basis of their likelihood to develop conduct disorder problems as calculated by the Strengths and Difficulties Questionnaire. While the inability of this study to distinguish between the Early and A-O subtypes of conduct disorder problems is certainly a limitation, the overall contribution of this

finding should not be undermined by this. This study shows that even when working with data from adolescent males with sub-clinical conduct disorder traits, one can observe one of the most replicated findings in the neuroimaging literature regarding CD problems: amygdala hypoactivity. One benefit of this finding is that amygdala hypoactivity in males with CD problems may now be used as a biomarker to investigate longitudinal predictive associations with various clinical and behavioural phenotypes at age 16, and at age 18 within Imagen. This would mean one can assess the extent to which neuroimaging findings might be used as biomarkers for negative outcomes associated with CD problems.

In terms of neuroimaging paradigms, it would have been preferable to have included an emotional reactivity task that showed participants a range of emotions and in particular fearfulness and sadness, rather than just anger. This would have allowed this study to better explore the deficits associated with CD problems plus CU traits in the context of fear or sadness processing, and would have meant that the extent to which control participants with high CU traits might also show the same aberrant amygdala reactivity could have been investigated.

In terms of the paradigm used in this study, and the subsequent contrast used, while the directionality of the results go in the expected direction; CD males showed reduced amygdala response compared to Control males, the inferences we might draw from these results are limited due to the non-face visual baseline used. In neuroimaging analysis the optimal situation would have been to use a contrast where the effects of viewing a neutral face were subtracted. This would leave all the information associated with viewing an angry face only, rather than face processing more generally. As the amygdala was the candidate region of interest and responds to novelty, as well as more specifically emotional stimuli, it would have been preferable to subtract the effects of the ambiguous faces from the angry ones. It may not

necessarily be the case that the participants interpreted the ambiguous faces as non-neutral, or threatening in some way, rather the significant amygdala activation is quite possibly a symptom of the presentation of a novel, interesting stimulus. In fact there is a growing body of evidence supporting this notion. A recent investigation by Balderston, Schultz and Helmstetter (2011) set out to characterise which aspects of stimuli were most associated to amygdala responses to novelty. The authors found that at both the whole brain and region of interest level of analysis, that the amygdala showed a significant response to novelty (faces and scenes), that was not moderated by the emotional nature of the stimulus. Crucially this study showed that the amygdala responds to novel neutral faces.

Despite this compelling evidence that the amygdala responds generally, to novel stimuli, there is still a possibility that the participants perceived the stimuli as threatening. A study by Adams and Kleck (2002) found that the direction of gaze can influence the perceived emotion of others, finding that faces with direct gaze were more readily identified as angry than those with averted gaze. In this particular paradigm all of the faces displayed have direct gaze to the participants, so it is possible that the participants might have interpreted the ambiguous faces as aversive. One way to investigate this proposition would be to explore the extent to which participants rate the ambiguous faces as emotional - be it negative or neutral. For instance using a likert style rating scale to explore how they themselves interpret the emotion, or lack of, while they were in the scanner. In the interim, the analysis could be improved by working with data from an angry vs. ambiguous contrast, to more specifically examine the effects of viewing anger as an emotion and making the results more readily interpretable.

It would have also been optimal to have worked with a task where both reward and punishment were explicitly examined. This study found evidence suggesting that there might have been some potentially interesting effects related to the omission of reward, the most

similar phase of reward processing to punishment; however the current findings would need to be tested in a paradigm specifically geared to assessing rewarding and punishing stimuli to make more concrete inferences.

*Identification of adolescents with 'High' CU traits*

One methodological limitation of this study was the threshold used for the identification of individuals with 'High CU'. Participants were classed as 'High CU' if they scored more than one standard deviation above the mean of the entire cohort, and were compared to the remaining participants who were classed as 'Average CU'. While this threshold might be regarded as lenient the decision to apply it at this level is in line with approaches used by other research groups. Some groups have applied a median split as a method of identifying individuals with 'High' CU traits (Jones *et al.,*2010; Schwenck *et al.,*2012; Viding *et al.,*2012), others have selected the top one third (Pasalich *et al.,*2012) while others have selected the top 10% (Barker, Oliver *et al.,*2011). It would of course have been optimal to directly compare adolescents with High CU to those with Low CU; however this would have resulted in small sample sizes and might have left the study insufficiently powered to detect meaningful between-group differences. Future research would therefore preferentially sample individuals with low CU in order to compare extreme groups; one could do this by using the top 25% and bottom 25% or alternatively working with the top and bottom thirds, however this is strongly dependent on the distribution of the CU trait and also CD symptoms across the sample in question.

*Pubertal Development*

Adolescence is characterised by considerable physical, social and cognitive development. It is a particularly delicate developmental period due to the extensive biological changes the brain

goes through during this time (Giedd, 2004), which are critical for establishing normal adult brain function. In a review of puberty-related influences on brain development Giedd and colleagues (2006) report a number of developmental differences between males and females. For instance, the total cerebral volume peaks later in boys (around 14 years old) compared to girls (around 11 years old) and the developmental trajectory of brain structures are difference in boys and girls. As such some of the neuroimaging findings in this thesis, particularly the finding in the inferior frontal gyrus in Chapter 5, are currently limited in terms of inference as the analyses did not take into consideration differences in pubertal stage in males and females. To ensure that between group differences in patterns of functional activation are not associated with differences in pubertal development stage, the analyses would need to be repeated, controlling for differences in development, or matching participants more closely.

*Socioeconomic Status*

One of the most commonly reported risk factors for the development of CD problems is social disadvantage as measured by socioeconomic status. Studies have reliably found that low socioeconomic status is significantly associated with CD problems (Oliver, Kretschmer and Maughan, 2013; Murray and Farrington, 2010; Barker *et al.,*2011). As differences in socioeconomic status are such an important risk factor for the development of CD problems it represents a real limitation of this study that these differences were not investigated or controlled for in the analyses. Prior to wider dissemination of the findings the relative contribution of SES as a control variable would need to be explored and then controlled for where necessary. In the meanwhile the extent to which the between inferences from the group differences may be interpreted and expanded on should be taken with caution.

*Future Directions*

Despite these limitations the studies reported in this thesis are of value. The study sample was large enough to enable meaningful comparisons to be made between males and females with CD; and was one of the first projects to do so with sufficient power.

Some of the potential future directions have already been alluded to throughout this thesis and in this chapter. An obvious next step would be to conduct similar investigations using dimensional symptom count data at age 14. Dimensional data could then be used to identify the longitudinal associations between CD and CU from age 14 to age 16. In particular the predictive value of the CU trait could be assessed and any association with negative outcomes at 16, as a function of gender, identified. Such a study could test the hypothesis that CU might act as an independent predictor or risk-factor for the development of internalising problems in control participants and would mean that baseline levels of CD symptoms could be controlled for.

In order to refine the conduct disorder phenotype there are a number of approaches one could take. Ideally, one would work with data from a community recruited longitudinal birth cohort that is large enough to contain a sufficient number of individuals that have both clinically significant levels of symptoms, sub-threshold symptoms, and a large group of unaffected control participants. Using this approach would mean that a sub-sample of the cohort could be invited to participate in further assessments e.g. neuropsychological experiments, on the basis of their CD and CU scores. In an ideal situation the sample would contain enough data points to allow individuals who score high versus those who score low for CU traits to be directly compared to one another. This type of sampling would also mean that there would be a large enough overlap between the High vs. Low CU trait and also a Case vs.

Control group of CD youths. Inviting a group of pre-selected individuals to participate in an additional investigation may mean that the usual challenges associated with small sample sizes are overcome, that is assuming all the participants wish to take part of course!

## 7.5 **Final Conclusions**

The evidence presented in this thesis suggests that males and females with CD problems are not the same as one another. In some domains there are striking similarities; they experience similarly comorbid levels of hyperactivity, peer relationship difficulties and personality traits such as hopelessness and impulsivity. Males and females also appear to show similar deficits on some tasks of executive function such as working memory. However when they are examined more closely, at the neurobiological level, and when additional variables such as callous unemotional traits are also investigated their profiles become far more complex.

Males appear to more readily fit into the theories and contexts already known about conduct disorder; they are more reward oriented (MID Task) and seem to show blunted affect in response to threat (emotional reactivity task). Females, however, appear punishment sensitive (MID Task) and show what appears to be a heightened response to threat (emotional reactivity task), which were effects that were not expected at the start of this study. Importantly, this study lends further weight to the use of the CU specifier not only for conduct problems, but as a trait assessment that shows huge potential utility across the general population. This thesis also suggests that wherever possible studies should attempt to recruit both males and females when investigating CD problems as they appear to show considerable differences to one another, especially in terms of neurofunctional reactivity.

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# Appendices

## 7.6 Appendix Chapter 2

**Strengths and Difficulties Questionnaire**

The information below is reproduced from the pdf documents available on the SDQ website http://www.sdqinfo.org/py/sdqinfo/b3.py?language=Englishqz(UK) .
Parent Rated

**Scoring the Informant-Rated Strengths and Difficulties Questionnaire**

The 25 items in the SDQ comprise 5 scales of 5 items each. It is usually easiest to score all 5 scales first before working out the total difficulties score. Somewhat True is always scored as 1, but the scoring of Not True and Certainly True varies with item, as shown below scale by scale. For each of the 5 scales the score can range from 0 to 10 if all 5 items were completed. Scale score can be prorated if at least 3 items were completed.

| **Emotional Symptoms Scale** | **Not True** | **Somewhat True** | **Certainly True** |
|---|---|---|---|
| Often complains of headaches, stomach-aches… | 0 | 1 | 2 |
| Many worries, often seems worried | 0 | 1 | 2 |
| Often unhappy, downhearted or tearful | 0 | 1 | 2 |
| Nervous or clingy in new situations… | 0 | 1 | 2 |
| Many fears, easily scared | 0 | 1 | 2 |
| **Conduct Problems Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| Often has temper tantrums or hot tempers | 0 | 1 | 2 |
| Generally obedient, usually does what… | 2 | 1 | 0 |
| Often fights with other children or bullies them | 0 | 1 | 2 |
| Often lies or cheats | 0 | 1 | 2 |
| Steals from home, school or elsewhere | 0 | 1 | 2 |
| **Hyperactivity Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| Restless, overactive, cannot stay still for long | 0 | 1 | 2 |
| Constantly fidgeting or squirming | 0 | 1 | 2 |
| Easily distracted, concentration wanders | 0 | 1 | 2 |
| Thinks things out before acting | 2 | 1 | 0 |
| Sees tasks through to the end, good attention span | 2 | 1 | 0 |
| **Peer Problems Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| Rather solitary, tends to play alone | 0 | 1 | 2 |
| Has at least one good friend | 2 | 1 | 0 |
| Generally liked by other children | 2 | 1 | 0 |
| Picked on or bullied by other children | 0 | 1 | 2 |
| Gets on better with adults than with other children | 0 | 1 | 2 |
| **Prosocial Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| Considerate of other people's feelings | 0 | 1 | 2 |

| | | | |
|---|---|---|---|
| Shares readily with other children | 0 | 1 | 2 |
| Helpful if someone is hurt, upset or feeling ill | 0 | 1 | 2 |
| Kind to younger children | 0 | 1 | 2 |
| Often volunteers to help others | 0 | 1 | 2 |

The Total Difficulties Score:

Is generated by summing scores from all the scales except the prosocial scale. The resultant score can range from 0 to 40 (and is counted as missing if one of the component scores is missing).

**Interpreting Symptom Scores and Defining "Caseness" from Symptom Scores**

Although SDQ scores can often be used as continuous variables, it is sometimes convenient to classify scores as normal, borderline and abnormal. Using the bandings shown below, an abnormal score on one or both of the total difficulties scores can be used to identify likely "cases" with mental health disorders. This is clearly on a rough-and ready method for detecting disorders - combining information from SDQ symptom and impact scores from multiple informants is better, but still far from perfect. Approximately 10% of a community sample scores in the abnormal band on any given score, with a further 10% scoring in the borderline band. The exact proportions vary according to country, age, and gender - normative SDQ data are available from the web site. You may want to adjust banding and caseness criteria for these characteristics, setting the threshold higher when avoiding false positives is of paramount importance, and setting the threshold lower when avoiding false negatives is more important.

| **Parent Completed** | **Normal** | **Borderline** | **Abnormal** |
|---|---|---|---|
| Total Difficulties Score | 0-13 | 14-16 | 17-40 |
| Emotional Symptoms Score | 0-3 | 4 | 5-10 |
| Conduct Problems Score | 0-2 | 3 | 4-10 |
| Hyperactivity Score | 0-5 | 6 | 7-10 |
| Peer Problems Score | 0-2 | 3 | 4-10 |
| Prosocial Behaviour Score | 6-10 | 5 | 0-4 |
| | | | |
| **Teacher Completed** | **Normal** | **Borderline** | **Abnormal** |
| Total Difficulties Score | 0-11 | 12-15 | 16-40 |
| Emotional Symptoms Score | 0-4 | 5 | 6-10 |
| Conduct Problems Score | 0-2 | 3 | 4-10 |
| Hyperactivity Score | 0-5 | 6 | 7-10 |
| Peer Problems Score | 0-3 | 4 | 5-10 |
| Prosocial Behaviour Score | 6-10 | 5 | 0-4 |

**Generating and Interpreting Impact Scores**

When using a version of the SDQ that includes an "Impact Supplement", the items on overall distress and social impairment can be summed to generate an impact score that ranges from 0-10 for the parent-completed version and from 0-6 for the teacher-completed version.

| Parent report | Not at all | Only a little | Quite a lot | A great deal |
|---|---|---|---|---|
| Difficulties upset or distress child | 0 | 0 | 1 | 2 |
| Interfere with HOME LIFE | 0 | 0 | 1 | 2 |
| Interfere with FRIENDSHIPS | 0 | 0 | 1 | 2 |
| Interfere with CLASSROOM LEARNING | 0 | 0 | 1 | 2 |
| Interfere with LEISURE ACTIVITIES | 0 | 0 | 1 | 2 |
| | | | | |
| **Teacher report** | **Not at all** | **Only a little** | **Quite a lot** | **A great deal** |
| Difficulties upset or distress child | 0 | 0 | 1 | 2 |
| Interfere with PEER RELATIONSHIPS | 0 | 0 | 1 | 2 |
| Interfere with CLASSROOM LEARNING | 0 | 0 | 1 | 2 |

Responses to the questions on chronicity and burden to others are not included in the impact score. When respondents have answered "no" to the first question on the impact supplement (i.e. when do they not perceive the child as having any emotional or behavioural difficulties), they are not asked to complete the questions on resultant distress or impairment; the impact score is automatically scored zero in these circumstances.

Although the impact scores can be used as continuous variables, it is sometimes convenient to classify them as normal, borderline or abnormal: a total impact score of 2 or more is abnormal; a score of 1 is borderline; and a score of 0 is normal.

**Adolescent Rated**

**Scoring the Self-Report Strengths and Difficulties Questionnaire**

The 25 items in the SDQ comprise 5 scales of 5 items each. It is usually easiest to score all 5 scales first before working out the total difficulties score. Somewhat True is always scored as 1, but the scoring of Not True and Certainly True varies with item, as shown below scale by scale. For each of the 5 scales the score can range from 0 to 10 if all 5 items were completed. Scale scores can be prorated if at least 3 items were completed.

| **Emotional Symptoms Scale** | **Not True** | **Somewhat True** | **Certainly True** |
|---|---|---|---|
| I get a lot of headaches, stomach-aches or sickness | 0 | 1 | 2 |
| I worry a lot | 0 | 1 | 2 |
| I am often unhappy, downhearted or tearful | 0 | 1 | 2 |
| I am nervous in new situations | 0 | 1 | 2 |
| I have many fears, I am easily scared | 0 | 1 | 2 |
| **Conduct Problems Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| I get very angry and often lose my temper | 0 | 1 | 2 |
| I usually do as I am told | 2 | 1 | 0 |
| I fight a lot | 0 | 1 | 2 |
| I am often accused of lying or cheating | 0 | 1 | 2 |
| I take things that are not mine | 0 | 1 | 2 |
| **Hyperactivity Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| I am restless. I cannot stay still for long | 0 | 1 | 2 |
| I am constantly fidgeting or squirming | 0 | 1 | 2 |

| | | | |
|---|---|---|---|
| I am easily distracted | 0 | 1 | 2 |
| I think before I do things | 2 | 1 | 0 |
| I finish the work I am doing | 2 | 1 | 0 |
| **Peer Problems Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| I am usually on my own | 0 | 1 | 2 |
| I have one good friend or more | 2 | 1 | 0 |
| Other people my age generally like me | 2 | 1 | 0 |
| Other children or young people pick on me | 0 | 1 | 2 |
| I get on better with adults than with people my age | 0 | 1 | 2 |
| **Prosocial Scale** | **Not True** | **Somewhat True** | **Certainly True** |
| I try to be nice to other people | 0 | 1 | 2 |
| I usually share with others | 0 | 1 | 2 |
| I am helpful if someone is hurt, upset or feeling ill | 0 | 1 | 2 |
| I am kind to younger children | 0 | 1 | 2 |
| I often volunteer to help others | 0 | 1 | 2 |

**The Total Difficulties Score**

Is generated by summing the scores from all the scales except the prosocial scale. The resultant score can range from 0 to 40 (and is counted as missing if one of the component scores is missing).

**Interpreting Symptom Scores and Defining "Caseness" from Symptom Scores**

Although the SDQ scores can often be used as continuous variables, it is sometimes convenient to classify scores as normal, borderline and abnormal. Using the bandings shown below, an abnormal score on the total difficulties score can be used to identify likely "cases" with mental health disorders. This is clearly only a rough-and ready method for detecting disorders - combining information from SDQ symptom and impact scores from multiple informants is better, but still far from perfect. Approximately 10% of a community sample scores in the abnormal band on any given score, with a further 10% scoring in the borderline band. The exact proportions vary according to country, age and gender - normative SDQ data are available from the web site. You may want to adjust banding and caseness criteria for these characteristics, setting the threshold higher when avoiding false positives is of paramount importance, and setting the threshold lower when avoiding false negatives is more important.

| **Self-Completed** | **Normal** | **Borderline** | **Abnormal** |
|---|---|---|---|
| Total Difficulties Score | 0-15 | 16-19 | 20-40 |
| Emotional Symptoms Score | 0-5 | 6 | 7-10 |
| Conduct Problems Score | 0-3 | 4 | 5-10 |
| Hyperactivity Score | 0-5 | 6 | 7-10 |
| Peer Problems Score | 0-3 | 4-5 | 6-10 |
| Prosocial Behaviour Score | 6-10 | 5 | 0-4 |

**Generating and Interpreting Impact Scores**

When using a version of the SDQ that includes an "Impact Supplement", the items on overall distress and social impairment can be summed to generate and impact score that ranges from 0-10.

| | **Not at all** | **Only a little** | **Quite a lot** | **A great deal** |
|---|---|---|---|---|
| Difficulties upset or distress me | 0 | 0 | 1 | 2 |
| Interfere with HOME LIFE | 0 | 0 | 1 | 2 |
| Interfere with FRIENDSHIPS | 0 | 0 | 1 | 2 |
| Interfere with CLASSROOM LEARNING | 0 | 0 | 1 | 2 |
| Interfere with LEISURE ACTIVITIES | 0 | 0 | 1 | 2 |

Responses to the questions on chronicity and burden to others are not included in the impact score. When respondents have answered "no" to the first question on the impact supplement (i.e. when they do not perceive themselves as having any emotional or behavioural difficulties), they are not asked to complete the questions on resultant distress or impairment; the impact score is automatically scored zero in these circumstances.

Although the impact scores can be used as continuous variables, it is sometimes convenient to classify them as normal, borderline or abnormal: a total impact score of 2 or more is abnormal; a score of 1 is borderline and a score of 0 is normal.

*SDQ Conduct Disorder Problem 'Caseness' Calculation*

For IMAGEN adolescents to be classed as "possible" cases of conduct disorder the parent had to rate the adolescent with ≥4 points, OR the adolescent rated themself as ≥5 points. For the adolescents to be "probable" cases they had to satisfy one of the following rules:

Parent rated score ≥5 and parent rated impact score is 2 OR

Adolescent rated score ≥6 and adolescent rated impact score is 2

**Substance Use Risk Profile Scale (SURPS)**

*Hopelessness*

| Item | Strongly Disagree | Disagree | Agree | Strongly Agree |
|---|---|---|---|---|
| I am content | 4 | 3 | 2 | 1 |
| I am happy | 4 | 3 | 2 | 1 |
| I have faith that my future holds great promise | 4 | 3 | 2 | 1 |
| I feel proud of my accomplishments | 4 | 3 | 2 | 1 |
| I feel that I'm a failure | 1 | 2 | 3 | 4 |
| I feel pleasant | 4 | 3 | 2 | 1 |
| I am very enthusiastic about my future | 4 | 3 | 2 | 1 |

*Impulsivity*

| Item | Strongly Disagree | Disagree | Agree | Strongly Agree |
|---|---|---|---|---|
| I often I often don't think things through before I speak | 1 | 2 | 3 | 4 |
| I often involve myself in situations that I later regret being involved in | 1 | 2 | 3 | 4 |
| I usually act without stopping to think | 1 | 2 | 3 | 4 |
| Generally, I am an impulsive person | 1 | 2 | 3 | 4 |
| I feel I have to be manipulative to get what I want | 1 | 2 | 3 | 4 |

**NEO-PI-R**

*Neuroticism*

| Item | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I am not a worrier | 4 | 3 | 2 | 1 | 0 |
| I often feel that I'm not as good as others | 0 | 1 | 2 | 3 | 4 |
| When I'm under a great deal of stress, sometimes I feel like I'm going to pieces | 0 | 1 | 2 | 3 | 4 |
| I rarely feel lonely or blue | 4 | 3 | 2 | 1 | 0 |
| I often feel tense and jittery | 0 | 1 | 2 | 3 | 4 |
| Sometimes I feel completely worthless | 0 | 1 | 2 | 3 | 4 |
| I rarely feel fearful or anxious | 4 | 3 | 2 | 1 | 0 |
| I often get angry at the way people treat me | 0 | 1 | 2 | 3 | 4 |
| Too often, when things go wrong, I get discouraged and feel like giving up | 0 | 1 | 2 | 3 | 4 |
| I am seldom sad or depressed | 4 | 3 | 2 | 1 | 0 |
| I often feel helpless and want someone else to solve my problems | 0 | 1 | 2 | 3 | 4 |
| At times I have been so ashamed I just wanted to hide | 0 | 1 | 2 | 3 | 4 |

*Extraversion*

| Item | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I like to have a lot of people around me | 0 | 1 | 2 | 3 | 4 |
| I laugh easily | 0 | 1 | 2 | 3 | 4 |
| I'm not happy-go-lucky | 4 | 3 | 2 | 1 | 0 |
| I really enjoy talking to people | 0 | 1 | 2 | 3 | 4 |
| I like to be where the action | 0 | 1 | 2 | 3 | 4 |
| I usually prefer to do things alone | 4 | 3 | 2 | 1 | 0 |
| I often feel as if I'm bursting with energy | 0 | 1 | 2 | 3 | 4 |
| I am a cheerful, high-spirited person | 0 | 1 | 2 | 3 | 4 |
| I am not a cheerful optimist | 4 | 3 | 2 | 1 | 0 |
| My life is fast-paced | 0 | 1 | 2 | 3 | 4 |
| I am a very active person | 0 | 1 | 2 | 3 | 4 |
| I would rather go my own way than be a leader of others | 4 | 3 | 2 | 1 | 0 |

*Openness*

| Item | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I don't like to waste my time daydreaming | 4 | 3 | 2 | 1 | 0 |
| Once I find the right way to do something, I stick to it | 4 | 3 | 2 | 1 | 0 |
| I am intrigued by the patterns I find in art and nature | 0 | 1 | 2 | 3 | 4 |
| I believe letting students hear controversial speakers can only confuse and mislead them | 4 | 3 | 2 | 1 | 0 |
| Poetry has little or no effect on me | 4 | 3 | 2 | 1 | 0 |
| I often try new and foreign foods | 0 | 1 | 2 | 3 | 4 |
| I seldom notice the moods or feelings that different environments produce | 4 | 3 | 2 | 1 | 0 |
| I believe we should look to our religious authorities for decisions on moral issues | 4 | 3 | 2 | 1 | 0 |
| Sometimes when I am reading poetry or looking at a work of art, I feel a chill or wave of excitement | 0 | 1 | 2 | 3 | 4 |
| I have little interest in speculating on the nature of the universe or human condition | 4 | 3 | 2 | 1 | 0 |
| I have a lot of intellectual curiosity | 0 | 1 | 2 | 3 | 4 |
| I often enjoy playing with theories or abstract ideas | 0 | 1 | 2 | 3 | 4 |

*Agreeableness*

| Item | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I try to be courteous to everyone I meet | 0 | 1 | 2 | 3 | 4 |
| I often get into arguments with my family and co-workers | 4 | 3 | 2 | 1 | 0 |
| Some people think I'm selfish and egotistical | 4 | 3 | 2 | 1 | 0 |
| I would rather cooperate with others than compete with them | 0 | 1 | 2 | 3 | 4 |
| Often, people aren't as nice as they seem to be | 4 | 3 | 2 | 1 | 0 |
| I believe that most people will take advantage of you if you let them | 4 | 3 | 2 | 1 | 0 |
| Most people I know like me | 0 | 1 | 2 | 3 | 4 |
| Some people think of me as cold and calculating | 4 | 3 | 2 | 1 | 0 |
| I don't worry much about the homeless | 4 | 3 | 2 | 1 | 0 |
| I generally try to be thoughtful and considerate | 0 | 1 | 2 | 3 | 4 |
| If I don't like people, I let them know it | 4 | 3 | 2 | 1 | 0 |
| If necessary, I am willing to manipulate people to get what I want | 4 | 3 | 2 | 1 | 0 |

*Conscientiousness*

| Item | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I keep my belongings neat and clean | 0 | 1 | 2 | 3 | 4 |
| I'm pretty good about pacing myself so as to get things done on time | 0 | 1 | 2 | 3 | 4 |
| I'm not a very orderly or methodical person | 4 | 3 | 2 | 1 | 0 |
| I try to perform all the tasks assigned to me conscientiously | 0 | 1 | 2 | 3 | 4 |
| I have a clear set of goals and work toward them in an orderly fashion | 0 | 1 | 2 | 3 | 4 |
| I waste a lot of time before settling down to work | 4 | 3 | 2 | 1 | 0 |
| I work hard to accomplish my goals | 0 | 1 | 2 | 3 | 4 |
| When I make a commitment, I can always be counted on to follow through | 0 | 1 | 2 | 3 | 4 |
| Sometimes I'm not as dependable or reliable as I should be | 4 | 3 | 2 | 1 | 0 |
| I am a productive person who always gets the job done | 0 | 1 | 2 | 3 | 4 |
| I never seem to be able to get organized | 4 | 3 | 2 | 1 | 0 |
| I strive for excellence in everything I do | 0 | 1 | 2 | 3 | 4 |

**Interpersonal Reactivity Index (IRI)**

*Empathic Concern*

| Item | Strongly Disagree | Disagree | Neither Agree nor Disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I often have tender, concerned feelings for people less fortunate than me. | 0 | 1 | 2 | 3 | 4 |
| Sometimes I don't feel very sorry for other people when they are having problems | 4 | 3 | 2 | 1 | 0 |
| When I see someone being taken advantage of, I feel kind of protective towards them | 0 | 1 | 2 | 3 | 4 |
| Other people's misfortunes do not usually disturb me a great deal | 4 | 3 | 2 | 1 | 0 |
| When I see someone being treated unfairly, I sometimes don't feel very much pity for them | 4 | 3 | 2 | 1 | 0 |
| I am often quite touched by things that I see happen | 0 | 1 | 2 | 3 | 4 |
| I would describe myself as a pretty soft-hearted person | 0 | 1 | 2 | 3 | 4 |

*Perspective Taking*

| Item | Strongly Disagree | Disagree | Neither Agree nor Disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I sometimes find it difficult to see things from the "other guy's" point of view | 4 | 3 | 2 | 1 | 0 |
| I try to look at everybody's side of a disagreement before I make a decision. | 0 | 1 | 2 | 3 | 4 |
| I sometimes try to understand my friends better by imagining how things look from their perspective | 0 | 1 | 2 | 3 | 4 |
| If I'm sure I'm right about something, I don't waste much time listening to other people's arguments | 4 | 3 | 2 | 1 | 0 |
| I believe that there are two sides to every question and try to look at them both. | 0 | 1 | 2 | 3 | 4 |
| When I'm upset at someone, I usually try to "put myself in his shoes" for a while | 0 | 1 | 2 | 3 | 4 |

| Item | Strongly Disagree | Disagree | Neither Agree nor Disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| Before criticizing somebody, I try to imagine how I would feel if I were in their place | 0 | 1 | 2 | 3 | 4 |

*Personal Distress*

| Item | Strongly Disagree | Disagree | Neither Agree nor Disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| In emergency situations, I feel apprehensive and ill-at-ease | 0 | 1 | 2 | 3 | 4 |
| I sometimes feel helpless when I am in the middle of a very emotional situation | 0 | 1 | 2 | 3 | 4 |
| When I see someone get hurt, I tend to remain calm | 4 | 3 | 2 | 1 | 0 |
| Being in a tense emotional situation scares me | 0 | 1 | 2 | 3 | 4 |
| I am usually pretty effective in dealing with emergencies | 4 | 3 | 2 | 1 | 0 |
| I tend to lose control during emergencies | 4 | 3 | 2 | 1 | 0 |
| When I see someone who badly needs help in an emergency, I go to pieces | 0 | 1 | 2 | 3 | 4 |

## fMRI Task Instructions

**Emotional Reactivity**

"In this task you will be presented with short video clips showing faces with neutral, happy and angry expressions as well as moving circles. Please watch them carefully and remember to lie as still as possible during this task."

**Stop Signal Reaction Time Task**

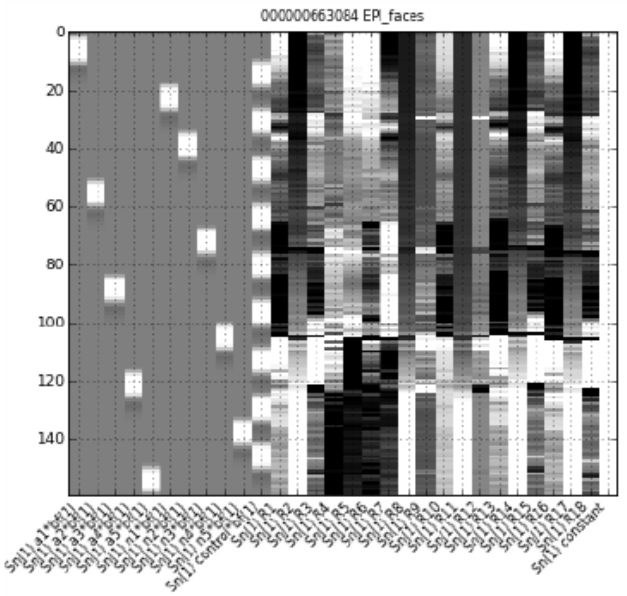
"In this task you will be presented with a picture of an arrow pointing left, or a picture of an arrow pointing right. You must respond by pressing the button with your left index finger if the arrow is pointing to the left and with your right index finger if the arrow is pointing to the right**.** It is important you react as quickly as possible. Occasionally the arrow pointing left or right will be followed by an arrow pointing upwards. If this happens, you must not respond at all, rather you must try and inhibit your reaction. Of course, you will not always be able to stop yourself from responding when this happens. Please do not wait to see if the upwards arrow is going to appear, the task is designed to allow for these mistakes."

**Monetary Incentive Delay**

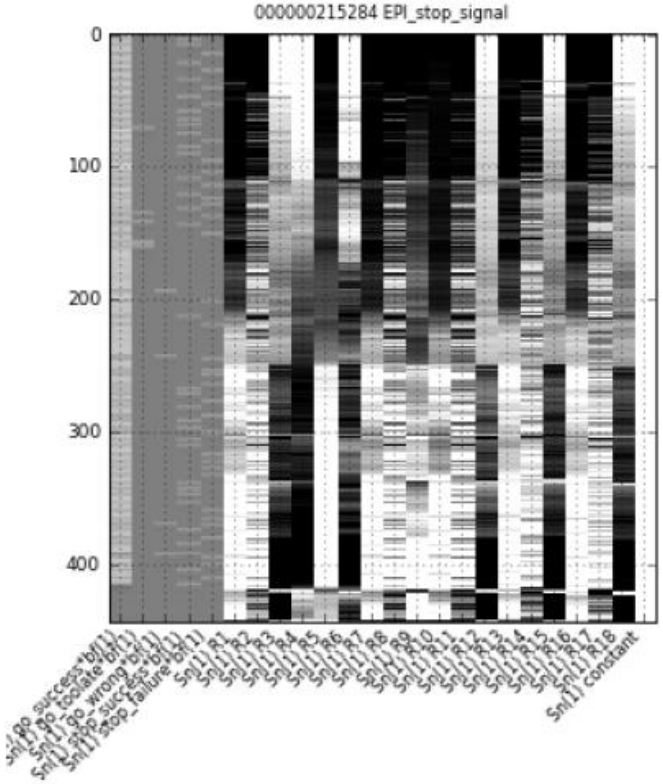
"The task is a reaction time task - it tests how quickly you can press the button to hit a target, which is a white square appearing only for a short time on the left or right of the screen. If you manage to press the button as soon as the white square appears, you will score points. If you respond too early (before the white square appears) or too late (after the white square has disappeared) you will not gain any points. You can tell where the white square will appear and how many points you will win by the symbol you see on the screen before the white square is shown. A triangle means you will not win any points, a circle with a l ine means you will win 2 points and a circle with three lines means you will win 10 points. You should try to win as many points as you can! - but only if you press the button while the square is presented on the screen! Your points will be exchanged for chocolates, let's see how many you can win!"

## fMRI Analysis: First Level Models

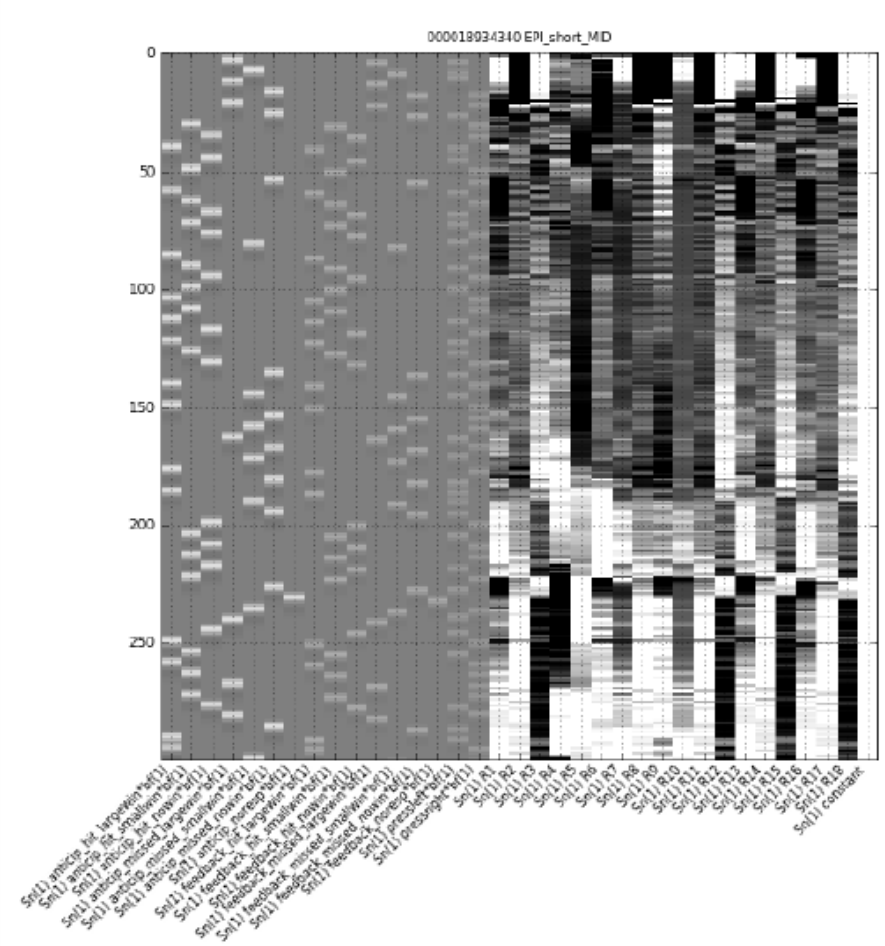
### Emotional Reactivity




### Stop Signal Reaction Time Task



**Monetary Incentive Delay**



## 7.7 **Appendix Chapter 3**

Table 55 Appendix Chapter Three Test Statistics: Demographic Variables

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F(1,1629)*** | ***eta²*** | **Contrast** | ***F(1,1629)*** | ***eta²*** | **Contrast** | ***F(1,1628)*** | ***eta²*** | **Contrast** | ***F(1,1629)*** | ***eta²*** | **Contrast** |
| Age | 0.50 | - | - | 0.01 | - | | 0.00 | - | - | 0.42 | - | - |
| Verbal IQ | 0.31 | - | - | 0.45 | - | - | 0.15 | - | - | 0.42 | - | - |
| Performance IQ | 0.11 | - | - | 0.17 | - | - | 1.22 | - | - | 0.35 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F(1,1629)*** | ***eta²*** | **Contrast** | ***F(1,1629)*** | ***eta²*** | **Contrast** | ***F(1,1629)*** | ***eta²*** | **Contrast** | | | |
| Age | 1.59 | - | - | 0.16 | - | - | 0.83 | - | - | | | |
| Verbal IQ | 23.19*** | 0.014 | Control > CD | 0.50 | - | - | 9.74** | 0.006 | M > F | | | |
| Performance IQ | 15.43*** | 0.009 | Control > CD | 2.32 | - | - | 0.05 | - | - | | | |

*$p$<0.05, **$p$<0.01, ***$p$<0.001

Table 56 Appendix Chapter Three Test Statistics (Interactions): Clinical and Temperamental Variables Age 14

| | Group-by-CU Interaction | | | Gender-by-Group Interaction | | | Gender-by-Group-by-CU Interaction | | | Gender-by-CU-Interaction | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** |
| Hyperactivity/Inattention | 3.92* (1,1629) | 0.002 | - | 1.97 (1,1629) | - | - | 0.07 (1,1628) | - | - | 4.76 (1,1629) | 0.003 | - |
| Emotional | 2.36 (1,1628) | - | - | 2.88 (1,1628) | - | - | 6.55*(1,1628) | 0.004 | - | 0.86 (1,1628) | - | - |
| Peer Relationship | 0.26 (1,1629) | - | - | 0.68 (1,1629 | - | - | 2.70 (1,1628) | - | - | 0.02 (1,1629) | - | - |
| Impulsivity | 0.10 (1,1629) | - | - | 1.13 (1,1629) | - | - | 0.00 (1,1628) | - | - | 1.84 (1,1629) | - | - |
| Hopelessness | 1.90 (1,1628) | - | - | 0.71 (1,1628) | - | - | 8.85**(1,1628) | 0.005 | - | 0.12 (1,1628) | - | - |

Table 57 Appendix Chapter Three Test Statistics (Main Effects): Clinical and Temperamental Variables Age 14

| | Main effect Group | | | Main effect CU | | | Main effect Gender | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** |
| Hyperactivity/Inattention | 183.12***(1,1629) | 0.101 | CD > Control | 0.104(1,1629) | - | - | 18.55***(1,1629) | 0.011 | M > F |
| Emotional | 8.65**(1,1628) | 0.003 | CD > Control | 3.35(1,1628) | - | - | 112.00***(1,1628) | 0.064 | F > M |
| Peer Relationship | 26.62***(1,1629) | 0.016 | CD > Control | 7.72**(1,1629) | 0.005 | High CU > Average CU | 4.55* (1,1629) | 0.003 | M > F |
| Impulsivity | 47.43***(1,1629) | 0.028 | CD > Control | 40.35***(1,1629) | 0.024 | High CU > Average CU | 3.31 (1,1629) | - | - |
| Hopelessness | 7.25** (1,1628) | 0.004 | CD > Control | 39.58 (1,1628) | 0.024 | High CU > Average CU | 11.20*** (1,1628) | 0.007 | F > M |

*$p$<0.05, **$p$<0.01, ***$p$<0.001

Table 58 Appendix Chapter Three Test Statistics (Interactions): Interpersonal Reactivity Index Variables Age 16

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** |
| Empathic Concern | 0.22(1,699) | - | - | 0.06 (1,699) | - | - | 0.46 (1,698) | - | - | 2.35 (1,699) | - | - |
| Personal Distress | 2.22 (1,699) | - | - | 6.10* (1,699) | 0.009 | - | 1.28 (1,698) | - | - | 1.37 (1,699) | - | - |
| Perspective Taking | 0.95 (1,699) | - | - | 0.01 (1,699) | - | - | 2.06 (1,698) | - | - | 0.12 (1,699) | - | - |

*$p$<0.05, **$p$<0.01, ***$p$<0.001

Table 59 Appendix Chapter Three Test Statistics (Main Effects): Interpersonal Reactivity Index Variables Age 16

| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** | ***F(df)*** | ***eta²*** | **Contrast** |
| Empathic Concern | 0.03 (1,699) | - | - | 26.37***(1,699) | 0.036 | Average CU > High CU | 18.93***(1,699) | 0.026 | F > M |
| Personal Distress | 1.56 (1,699) | - | - | 3.46 (1,699) | - | - | 30.19***(1,699) | 0.041 | F > M |
| Perspective Taking | 0.01 (1,699) | - | - | 10.74 (1,699) | 0.015 | Average CU > High CU | 0.78 (1,699) | - | - |

*$p$<0.05, **$p$<0.01, ***$p$<0.001

## 7.8 **Appendix Chapter 4**

Table 60 Appendix Chapter Four Test Statistics: Demographic Variables

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F*** | ***eta²*** | **Contrast** | ***F*** | ***eta²*** | **Contrast** | ***F*** | ***eta²*** | **Contrast** | ***F*** | ***eta²*** | **Contrast** |
| **Age** | 0.15*(1,1629)* | - | - | 0.19*(1,1629)* | - | - | 0.00*(1,1629)* | - | - | 0.00*(1,1629)* | - | - |
| **Verbal IQ** | 0.09(1,1573) | - | - | 0.49(1,1573) | - | - | 0.40(1,1572) | - | - | 0.10(1,1573) | - | - |
| **Performance IQ** | 0.06(1,1573) | - | - | 0.13(1,1573) | - | - | 2.21(1,1572) | - | - | 1.84(1,1573) | - | - |
| **Hyperactivity/Inattention** | 0.76(1,1629) | - | - | 3.84(1,1629) | - | - | 0.01(1,1628) | - | - | 4.24*(1,1629) | 0.003 | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| **Measure** | ***F*** | ***eta²*** | **Contrast** | ***F*** | ***eta²*** | **Contrast** | ***F*** | ***eta²*** | **Contrast** | | | |
| **Age** | 0.94*(1,1629)* | - | - | 0.97*(1,1629)* | - | - | 0.03*(1,1629)* | - | - | | | |
| **Verbal IQ** | 12.32***(1,1573) | - | Control > CD | 0.50(1,1573) | - | - | 7.42**(1,1573) | 0.005 | M > F | | | |
| **Performance IQ** | 12.40***(1,1573) | 0.008 | Control > CD | 2.16(1,1573) | - | - | 0.29(1,1573) | - | - | | | |
| **Hyperactivity/Inattention** | 187.34***(1,1629) | 0.103 | CD > Control | 0.63(1,1629) | - | - | 14.89***(1,1629) | 0.009 | M > F | | | |

****p*<.001, ***p*<.01, **p*<.05

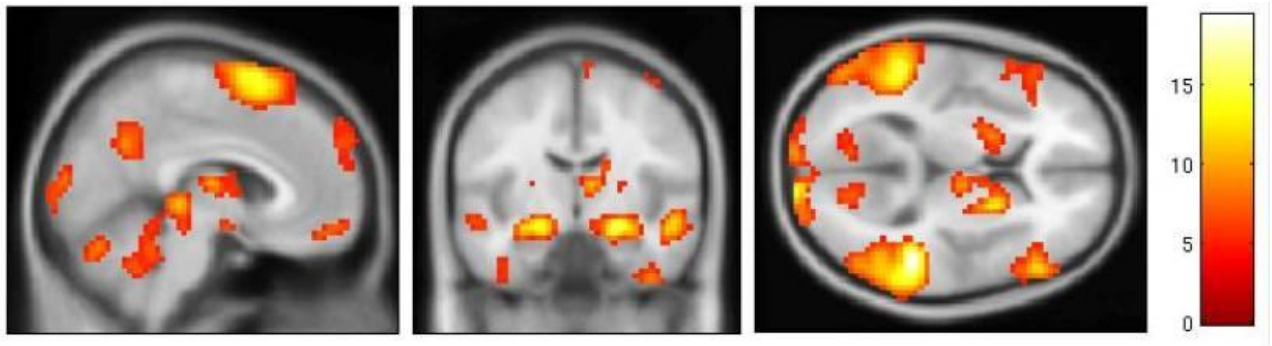



Figure 27 Random Effects Clusters for the Emotional Reactivity Task 'Ambiguous vs. Control Contrast' (Full Sample)

Table 61 Significant Random Effects Clusters for the Emotional Reactivity Task 'Ambiguous vs. Control Contrast' (Full Sample)

| **Full Sample Random effects analysis** | | | | | **Cluster** |
|---|---|---|---|---|---|
| **Brain Region of Activation (Peak and sub peaks reported)** | **BA** | **Talaraich (xyz)** | **Voxels** | ***Z*** | ***p*** |
| Middle Temporal Gyrus, Amygdala | | 51 -40 7 [21 -7 -14 / 42 -46 -23] | 6099 | Inf | <.001 |
| Amygdala, Thalamus, Temporal Pole, | 38 | -18 -7 -14 [ -1 -5 7 / -30 14 -35] | 455 | Inf | <.001 |
| Inferior Frontal Gyrus [pars opercularis & triangularis] | | 45 20 22 [51 5 52 / 39 14 28] | 1450 | Inf | <.001 |
| Superior Frontal Gyrus | | 6 14 67 [-6 2 73] | 488 | Inf | <.001 |
| Inferior Frontal Gyrus [pars opercularis & triangularis], Middle Frontal Gyrus, Precentral Gyrus | 6 | -45 17 25 [-42 -1 49 / -51 2 55] | 899 | Inf | <.001 |
| Precuneus | 31 | 6 -61 31 | 96 | Inf | 3.18e-14 |
| Medial Prefrontal Cortex | 10 | 6 50 -17 | 55 | 7.43 | 2.03e-10 |
| Frontal Pole | 9 | 9 65 37 [9 59 31 / 6 59 43] | 72 | 7.4 | 4.39e-1 |
| Intracalcarine Cortex, Lingual Gyrus | | 15 -76 7 | 39 | 7.29 | 1.1e-08 |
| Intracalcarine Cortex | | -9 -73 10 [-18 -76 7] | 26 | 7.16 | 4.31e-07 |
| Temporal Fusiform Cortex, Inferior Temporal Gyrus | | -39 -7 -41 | 26 | 6.21 | 4.31e-07 |

Table 62 Appendix Chapter Four Test Statistics: 'Angry vs. Control Contrast' Amygdala Region of Interest

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F(1,1628)*** | ***eta²*** | **Contrast** | ***F(1,1628)*** | ***eta²*** | **Contrast** | ***F(1,1627)*** | ***eta²*** | **Contrast** | ***F(1,1628)*** | ***eta²*** | **Contrast** |
| L AMYG | 0.44 | - | - | 0.80 | - | - | 0.15 | - | - | 0.70 | - | - |
| RAMYG | 0.02 | - | - | 6.68 | 0.004 | See[1] | 0.73 | - | - | 0.46 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F(1,1628)*** | ***eta²*** | **Contrast** | ***F(1,1628)*** | ***eta²*** | **Contrast** | ***F(1,1628)*** | ***eta²*** | **Contrast** | | | |
| L AMYG | 0.00 | - | - | 1.45 | - | - | 2.12 | - | - | | | |
| RAMYG | 0.73 | - | - | 2.57 | - | - | 1.55 | - | - | | | |

***$p$<.001, **$p$<.01, *$p$<.05

[1]Male Controls > Male CD*This effect remains when symptoms of Hyperactivity/Inattention, Emotional Symptoms and Verbal IQ Score are also controlled for $F$(1,1569) 5.76, $p$<.05 [Male Controls > Male CD*]

Table 63 Appendix Chapter Four Test Statistics: 'Ambiguous vs. Control Contrast' Amygdala Region of Interest

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F(1,1513)*** | ***eta²*** | **Contrast** | ***F(1,1513)*** | ***eta²*** | **Contrast** | ***F(1,1512)*** | ***eta²*** | **Contrast** | ***F(1,1513)*** | ***eta²*** | **Contrast** |
| L AMYG | 0.09 | - | - | 0.02 | - | - | 1.19 | - | - | 0.33 | - | - |
| RAMYG | 0.19 | - | - | 0.01 | - | - | 0.62 | - | - | 0.78 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F(1,1513)*** | ***eta²*** | **Contrast** | ***F(1,1513)*** | ***eta²*** | **Contrast** | ***F(1,1513)*** | ***eta²*** | **Contrast** | | | |
| L AMYG | 0.28 | - | - | 0.55 | - | - | 0.78 | - | - | | | |
| RAMYG | 0.01 | - | - | 0.16 | - | - | 0.33 | - | - | | | |

## 7.9 **Appendix Chapter 5**

Table 64 Appendix Chapter Five Test Statistics (Interactions): Demographic Variables

| | Group-by-CU Interaction | | | Gender-by-Group Interaction | | | Gender-by-Group-by-CU Interaction | | | Gender-by-CU-Interaction | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **Age** | 0.02 (1,1007) | - | - | 0.81 (1,1007) | - | - | 0.67 (1,1006) | - | - | 0.19(1,1007) | - | - |
| **Verbal IQ** | 0.00 (1,1007) | - | - | 0.09 (1,1007) | - | - | 0.33 (1,1006) | - | - | 0.01(1,1007) | - | - |
| **Performance IQ** | 1.65 (1,1007) | - | - | 0.00 (1,1007) | - | - | 0.41 (1,1006) | - | - | 0.55(1,1007) | - | - |
| **Hyperactivity/Inattention** | 0.25 (1,1007) | - | - | 0.78 (1,1007) | - | - | 0.21 (1,1006) | - | - | 0.33(1,1007) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 65 Appendix Chapter Five Test Statistics (Main Effects): Demographic Variables

| | Main Effect Group | | | Main effect Gender | | | Main Effect CU | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **Age** | 0.03 (1,1007) | - | - | 0.00 (1,1007) | - | - | 0.30 (1,1007) | - | - |
| **Verbal IQ** | 14.28***(1,1007) | 0.014 | Control > CD | 4.04* (1,1007) | 0.014 | M > F | 0.77 (1,1007) | - | - |
| **Performance IQ** | 1.33 (1,1007) | - | - | 0.14 (1,1007) | - | - | 0.73 (1,1007) | - | - |
| **Hyperactivity/Inattention** | 110.63*** (1,1007) | 0.099 | CD > Control | 5.39* (1,1007) | 0.005 | M > F | 0.15 (1,1007) | - | - |

Table 66 Appendix Chapter Five Test Statistics Gender-by-Group-by-CU Interaction: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 0.03 (1,885) | - | - | 0.12 (1,884) | - | - | 0.09 (1,883) | - | - |
| **SSRT Reaction Time (ms)** | 4.51 (1,537) | 0.008 | - | 4.52 (1,536) | 0.008 | - | 4.50 (1,535) | 0.008 | see 1 |
| **WISC (DSLB)** | 0.50 (1,1003) | - | - | 0.41 (1,1002) | - | - | 0.44 (1,1001) | - | - |
| **SWM Between-Errors** | 0.16 (1,1006) | - | - | 0.08 (1,1005) | - | - | 0.12 (1,1004) | - | - |
| **SWM Strategy Score** | 1.46 (1,1006) | - | - | 1.26 (1,1005) | - | - | 1.35 (1,1004) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001. 1 Despite the significant overall interaction effect there were no significant effects following correction for multiple comparison. In males with CD there was no main effect of CU $F$(1,35) 0.31, $p$>0.05. In control males there was no main effect of CU $F$(1,207) 0.12, $p$>0.05. In females with CD there was no main effect of CU $F$(1,23) 3.33, $p$>0.05. In control females there was no main effect of CU $F$(1,246) 0.46, $p$>0.05.

Table 67 Appendix Chapter Five Test Statistics Gender-by-Group Interaction: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 1.63 (1,886) | - | - | 1.53 (1,885) | - | - | 1.36 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.03 (1,538) | - | - | 0.04 (1,537) | - | - | 2.16 (1,535) | - | - |
| **WISC (DSLB)** | 2.13 (1,1004) | - | - | 1.95 (1,1003) | - | - | 1.86 (1,1002) | - | - |
| **SWM Between-Errors** | 0.50 (1,1007) | - | - | 0.44 (1,1006) | - | - | 0.34 (1,1005) | - | - |
| **SWM Strategy Score** | 0.69 (1,1007) | - | - | 0.81 (1,1006) | - | - | 0.90 (1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 68 Appendix Chapter Five Test Statistics Gender-by-CU Interaction: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 0.16 (1,886) | - | - | 0.17 (1,885) | - | - | 0.11 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.04 (1,538) | - | - | 0.04 (1,537) | - | - | 1.66 (1,535) | - | - |
| **WISC (DSLB)** | 1.09 (1,1004) | - | - | 1.24 (1,1003) | - | - | 0.11 (1,1002) | - | - |
| **SWM Between-Errors** | 0.05 (1,1007) | - | - | 0.04 (1,1006) | - | - | 0.02 (1,1005) | - | - |
| **SWM Strategy Score** | 1.11 (1,007) | - | - | 1.12 (1,1006) | - | - | 1.05 (1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 69 Appendix Chapter Five Test Statistics Group-by-CU Interaction: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 2.49 (1,886) | - | - | 2.52 (1,885) | - | - | 2.73 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.12 (1,538) | - | - | 0.12 (1,537) | - | - | 0.28 (1,535) | - | - |
| **WISC (DSLB)** | 0.07 (1,1004) | - | - | 0.09 (1,1003) | - | - | 0.11 (1,1002) | - | - |
| **SWM Between-Errors** | 0.06 (1,1007) | - | - | 0.06 (1,1006) | - | - | 0.09 (1,1005) | - | - |
| **SWM Strategy Score** | 0.41 (1,1007) | - | - | 0.43 (1,1006) | - | - | 0.39 (1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 70 Appendix Chapter Five Test Statistics Main Effect Gender: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 0.05 (1,886) | - | - | 0.00 (1,885) | - | - | 0.04 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.92 (1,538) | - | - | 0.96 (1,537) | - | - | 1.97 (1,535) | - | - |
| **WISC (DSLB)** | 1.35 (1,1004) | - | - | 0.44 (1,1003) | - | - | 0.60 (1,1002) | - | - |
| **SWM Between-Errors** | 1.87 (1,1007) | - | - | 0.96 (1,1006) | - | - | 1.60 (1,1005) | - | - |
| **SWM Strategy Score** | 0.24 (1,1007) | - | - | 0.02 (1,1006) | - | - | 0.09 (1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 71 Appendix Chapter Five Test Statistics Main Effect Group: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 6.81 (1,886) | 0.008 | CD > Control | 4.50* (1,885) | 0.005 | CD > Control | 1.65 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.98 (1,538) | - | - | 0.92 (1,537) | - | - | 0.05 (1,535) | - | - |
| **WISC (DSLB)** | 2.02 (1,1004) | - | - | 0.25 (1,1003) | - | - | 0.01 (1,1002) | - | - |
| **SWM Between-Errors** | 15.15***(1,1007) | 0.015 | CD > Control | 10.05**(1,1006) | 0.010 | CD > Control | 4.29*(1,1005) | 0.004 | CD > Control |
| **SWM Strategy Score** | 4.30*(1,1007) | 0.004 | CD > Control | 2.00 (1,1006) | - | - | 0.60(1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

Table 72 Appendix Chapter Five Test Statistics Main Effect CU: Neuropsychological Measures All Models

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Full Sample** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** | ***F (df)*** | ***eta²*** | **Contrast** |
| **SSRT Premature Responses** | 2.06 (1,886) | - | - | 2.39 (1,885) | - | - | 2.34 (1,884) | - | - |
| **SSRT Reaction Time (ms)** | 0.08 (1,538) | - | - | 0.10 (1,537) | - | - | 0.01 (1,535) | - | - |
| **WISC (DSLB)** | 1.27 (1,1004) | - | - | 0.72 (1,1003) | - | - | 0.77 (1,1002) | - | - |
| **SWM Between-Errors** | 0.01 (1,1007) | - | - | 0.08 (1,1006) | - | - | 0.05 (1,1005) | - | - |
| **SWM Strategy Score** | 0.02 (1,1007) | - | - | 0.00 (1,1006) | - | - | 0.00 (1,1005) | - | - |

Table 73 Appendix Chapter Five Test Statistics: Right Inferior Frontal Gyrus All Models

| | Gender-by-Group-by-CU | | | Gender-by-Group | | | Gender-by-CU | | | Group-by-CU | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F* (df)** | **eta²** | **Contrast** | ***F* (df)** | **eta²** | **Contrast** | ***F* (df)** | **eta²** | **Contrast** | ***F* (df)** | **eta²** | **Contrast** |
| **Model 1** | 0.27 (1,1006) | - | - | 6.64* (1,1007) | 0.007 | CD Male > CD Female | 0.61 (1,1007) | - | - | 0.12 (1,1007) | - | - |
| **Model 2** | 0.28 (1,1005) | - | - | 6.63* (1,1006) | 0.007 | CD Male > CD Female | 0.61 (1,1006) | - | - | 0.12 (1,1006) | - | - |
| **Model 3** | 0.29 (1,1004) | - | - | 6.72* (1,1005) | 0.007 | CD Male > CD Female | 0.63 (1,1005) | - | - | 0.11 (1,1005) | - | - |

| | Gender | | | Group | | | CU | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***F* (df)** | **eta²** | **Contrast** | ***F* (df)** | **eta²** | **Contrast** | ***F* (df)** | **eta²** | **Contrast** |
| **Model 1** | 3.29 (1,1007) | - | - | 0.21 (1,1007) | - | - | 2.30 (1,1007) | - | - |
| **Model 2** | 3.24 (1,1006) | - | - | 0.19 (1,1006) | - | - | 2.29 (1,1006) | - | - |
| **Model 3** | 2.98 (1,1005) | - | - | 0.41 (1,1005) | - | - | 2.24 (1,1005) | - | - |

*$p$<.05, **$p$<.01, ***$p$<.001

If the analysis is performed with only those individuals who made premature response errors on at least one trial (n899) the significant interaction effect remained; $F$(1,884) 4.96, $p$<.05, eta²0.006, males with CD showed significantly greater rIFG response compared to females with CD ($p$<.05), there were no additional significant effects. Note: all subject responses were recorded; Go Success, Go too late, Go wrong key response, stop failure, stop success, stop too early and summed to the total number of paradigm trials (n480). The number of people in this analysis are fewer as n121 individuals made no premature errors and were therefore not included in this analysis.

This analysis was repeated for the reduced sample matched to those individuals for whom SSRT reaction time data were available (n551); the significant interaction effect remained; $F$(1,536) 6.46, $p$<.05, eta²0.012; males with CD showed significantly greater rIFG response compared to females with CD ($p$<.05), there were no additional significant effects.

## 7.10 **Appendix Chapter 6**

Table 74 Appendix Chapter Six Test Statistics (Interactions): Demographic Variables

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | Contrast |
| Age | 0.35 | - | - | 0.38 | - | - | 0.97 | - | - | 0.61 | - | - |
| Verbal IQ | 1.84 | - | - | 0.12 | - | - | 0.16 | - | - | 0.26 | - | - |
| Performance IQ | 2.26 | - | - | 0.02 | - | - | 1.85 | - | - | 2.34 | - | - |
| Hyperactivity/Inattention Symptoms | 2.40 | - | - | 0.00 | - | - | 0.07 | - | - | 2.58 | - | - |

Table 75 Appendix Chapter Six Test Statistics (Main Effects): Demographic Variables

| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Measure** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | **Contrast** |
| Age | 0.29 | - | - | 0.28 | - | - | 0.09 | - | - |
| Verbal IQ | 3.03 | - | - | 1.43 | - | - | 5.06* | 0.01 | M > F |
| Performance IQ | 2.87 | - | - | 0.47 | - | - | 0.07 | - | - |
| Hyperactivity/Inattention Symptoms | 96.36*** | 0.08 | CD>Control | 0.45 | - | - | 17.65*** | 0.02 | M > F |

Table 76 Appendix Chapter Six Test Statistics (Main Effects and Interactions): Cambridge Gambling Task

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1023)*** | ***eta²*** | **Contrast** | ***F(1,1023)*** | ***eta²*** | **Contrast** | ***F(1,1022)*** | ***eta²*** | **Contrast** | ***F(1,1023)*** | ***eta²*** | **Contrast** |
| Proportion Bet | 0.15 | - | - | 0.14 | - | - | 1.41 | - | - | 2.68 | - | - |
| Risk Taking | 0.26 | - | - | 0.14 | - | - | 1.50 | - | - | 2.78 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F(1,1023)*** | ***eta²*** | **Contrast** | ***F(1,1023)*** | ***eta²*** | **Contrast** | ***F(1,1023)*** | ***eta²*** | **Contrast** | | | |
| Proportion Bet | 0.75 | - | - | 0.06 | - | - | 25.17*** | 0.024 | M > F | | | |
| Risk Taking | 0.70 | - | - | 0.00 | - | - | 31.08*** | 0.029 | M > F | | | |

Table 77 Appendix Chapter Six Test Statistics Main and Interaction Effects: Reward Anticipation Ventral Striatum

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** |
| LVS | 0.00 | - | - | 1.11 | - | - | 0.13 | - | - | 4.92* | 0.005 | see[1] |
| RVS | 0.01 | - | - | 2.60 | - | - | 0.12 | - | - | 3.75 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| LVS | 0.03 | - | - | 0.28 | - | - | 1.39 | - | - | | | |
| RVS | 0.31 | - | - | 2.88 | - | - | 0.00 | - | - | | | |

[1]In males High CU was associated with significantly greater mean LVS BOLD responses compared to Males with Low CU ($p<.05$). No effects in females.

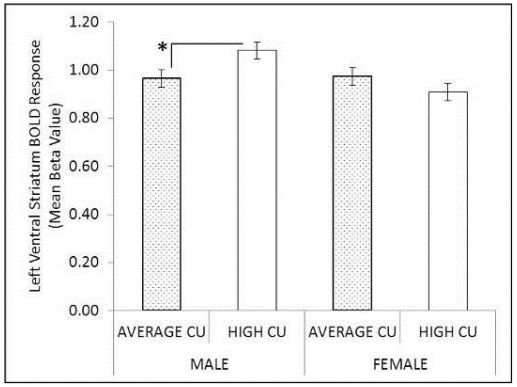



Figure 28 Region of Interest Analysis: Significant Gender-by-CU Interaction effect for the MID Task 'Anticipation Large Win vs. Anticipation No Win' Contrast in the Left Ventral Striatum, (*$p<.05$)

Table 78 Appendix Chapter Six Test Statistics Main and Interaction Effects: Reward Anticipation Amygdala

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1020)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** |
| LAMYG | 0.27 | - | - | 0.68 | - | - | 0.02 | - | - | 0.70 | - | - |
| RAMYG | 0.10 | - | - | 0.04 | - | - | 0.00 | - | - | 1.01 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| LAMYG | 2.78 | - | - | 0.13 | - | - | 2.68 | - | - | | | |
| RAMYG | 1.93 | - | - | 0.38 | - | - | 1.99 | - | - | | | |

Table 79 Appendix Chapter Six Test Statistics Main and Interaction Effects: Reward Anticipation MOFC

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** |
| L mOFC | 0.40 | - | - | 0.66 | - | - | 0.37 | - | - | 0.52 | - | - |
| R mOFC | 0.07 | - | - | 1.42 | - | - | 0.01 | - | - | 0.21 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| L mOFC | 0.95 | - | - | 0.38 | - | - | 0.55 | - | - | | | |
| R mOFC | 0.57 | - | - | 1.40 | - | - | 0.34 | - | - | | | |

Table 80 Appendix Chapter Six Test Statistics Main and Interaction Effects: Positive Reward Outcome Amygdala

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** |
| LAMYG | 0.84 | - | - | 1.14 | - | - | 2.58 | - | - | 0.33 | - | - |
| RAMYG | 1.29 | - | - | 0.01 | - | - | 0.34 | - | - | 1.26 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | | | |
| LAMYG | 0.76 | - | - | 0.03 | - | - | 1.03 | - | - | | | |
| RAMYG | 2.06 | - | - | 0.52 | - | - | 0.06 | - | - | | | |

Table 81 Appendix Chapter Six Test Statistics Main and Interaction Effects: Positive Reward Outcome Anterior Cingulate Cortex

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** |
| LACC | 1.69 | - | - | 0.26 | - | - | 0.15 | - | - | 0.18 | - | - |
| RACC | 1.20 | - | - | 0.31 | - | - | 0.10 | - | - | 0.14 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | ***F (1,1022)*** | ***eta²*** | **Contrast** | | | |
| LACC | 0.76 | - | - | 6.52* | 0.006 | Average > High | 0.00 | - | - | | | |
| RACC | 0.53 | - | - | 3.11 | - | - | 0.06 | - | - | | | |

Table 82 Appendix Chapter Six Test Statistics Main and Interaction Effects: Positive Reward Outcome MOFC

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1020)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** |
| L mOFC | 0.71 | - | - | 1.55 | - | - | 1.73 | - | - | 0.11 | - | - |
| R mOFC | 0.84 | - | - | 1.20 | - | - | 1.51 | - | - | 0.05 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| L mOFC | 2.32 | - | - | 2.59 | - | - | 0.00 | - | - | | | |
| R mOFC | 2.87 | - | - | 2.81 | - | - | 0.02 | - | - | | | |

Table 83 Appendix Chapter Six Test Statistics Main and Interaction Effects: Negative Reward Outcome Anterior Cingulate Cortex

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1020)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** |
| LACC | 0.30 | - | - | 1.54 | - | - | 2.57 | - | - | 0.06 | - | - |
| RACC | 0.33 | - | - | 1.55 | - | - | 2.60 | - | - | 0.46 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (2,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| LACC | 0.08 | - | - | 0.21 | - | - | 0.40 | - | - | | | |
| RACC | 0.79 | - | - | 0.48 | - | - | 0.20 | - | - | | | |

Table 84 Appendix Chapter Six Test Statistics Main and Interaction Effects: Negative Reward Outcome Insula

| | **Group-by-CU Interaction** | | | **Gender-by-Group Interaction** | | | **Gender-by-Group-by-CU Interaction** | | | **Gender-by-CU-Interaction** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** |
| L INS | 5.59* | 0.005 | see[1] | 5.42* | 0.005 | see[2] | 5.16* | 0.005 | See[3] | 0.03 | - | - |
| R INS | 5.28* | 0.005 | see[1] | 4.59* | 0.004 | see[2] | 4.07* | 0.004 | See[3] | 0.03 | - | - |
| | **Main effect Group** | | | **Main effect CU** | | | **Main effect Gender** | | | | | |
| | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | ***F (1,1021)*** | ***eta²*** | **Contrast** | | | |
| L INS | 2.91 | - | - | 0.15 | - | - | 0.01 | - | - | | | |
| R INS | 2.14 | - | - | 1.49 | - | - | 0.03 | - | - | | | |

[1]There was a nominally significant Group-by-CU interaction bilaterally in the insula (Left p= .018, Right p= .022), however these effects did not survive correction for multiple region of interest analysis (*p*>.012). In both hemispheres it appeared as though in the group with CD problems the group with High CU traits were significantly more responsive in the insula bilaterally in comparison to the Average CU group; however formal tests did not show any significant differences between the groups.

[2]There was a nominally significant Gender-by-Group interaction bilaterally in the insula (Left p=.020, Right p=.032), however the overall interaction effects also did not survive correction for multiple region of interest analysis (*p*>.012). In both hemispheres it appeared as though females with CD problems were significantly more responsive in the insula bilaterally in comparison to female controls; however formal tests did not show any significant differences between the groups.

[3]See Figures 29 and 30

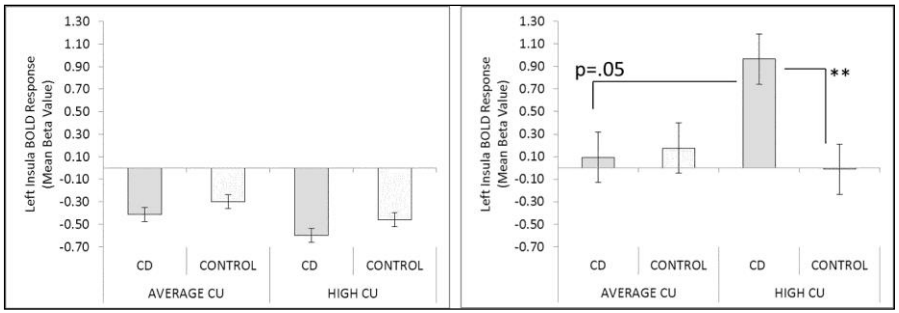



Figure 29 Region of Interest Analysis: Significant Gender-by-Group-by-CU Interaction effect for MID Task 'Feedback Failure Large Win vs. Feedback No Win in the Left Insula (Males Left, Females Right) *p*<.01**

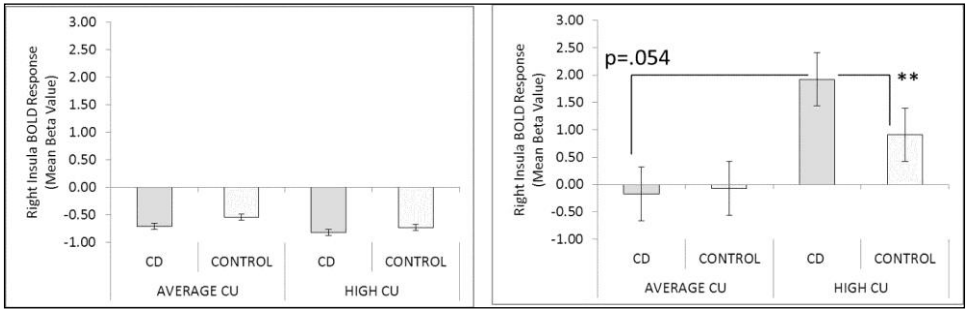



Figure 30 Region of Interest Analysis: Significant Gender-by-Group-by-CU Interaction effect for MID Task 'Feedback Failure Large Win vs. Feedback No Win in the Right Insula (Males Left, Females Right) *p*<.01**